Indole Cytosolic Phospholipase A_2 α Inhibitors: Discovery and in Vitro and in Vivo Characterization of 4-{3-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid, Efipladib

John C. McKew,*,† Katherine L. Lee,† Marina W. H. Shen,‡ Paresh Thakker,† Megan A. Foley,† Mark L. Behnke,† Baihua Hu,† Fuk-Wah Sum,† Steve Tam,† Yonghan Hu,† Lihren Chen,† Steven J. Kirincich,† Ronald Michalak,# Jennifer Thomason,† Manus Ipek,† Kun Wu,† Lane Wooder,† Manjunath K. Ramarao,‡ Elizabeth A. Murphy,‡ Debra G. Goodwin,‡ Leo Albert,‡ Xin Xu,§ Frances Donahue,# M. Sherry Ku,# James Keith,‡ Cheryl L. Nickerson-Nutter,‡ William M. Abraham,∇ Cara Williams,‡ Martin Hegen,‡ and James D. Clark‡

Departments of Chemical and Screening Sciences, Inflammation, Drug Safety and Metabolism, and Chemical and Pharmaceutical Development, Wyeth Research, 200 CambridgePark Drive, Cambridge, Massachusetts 02140, and Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, Florida 33140

Received November 21, 2007

The optimization of a class of indole cPLA$_2$α inhibitors is described herein. The importance of the substituent at C3 and the substitution pattern of the phenylmethane sulfonamide region are highlighted. Optimization of these regions led to the discovery of **111** (efipladib) and **121** (WAY-196025), which are shown to be potent, selective inhibitors of cPLA$_2$α in a variety of isolated enzyme assays, cell based assays, and rat and human whole blood assays. The binding of these compounds has been further examined using isothermal titration calorimetry. Finally, these compounds have shown efficacy when dosed orally in multiple acute and chronic prostaglandin and leukotriene dependent in vivo models.

Introduction

The arachidonic acid pathway is rich with targets for pharmaceutical intervention, and as such, selected enzymes and receptors have been successfully targeted in the past for the treatment of pain and asthma. New genetic data in humans and mice have led to renewed interest in additional targets in the arachidonic acid pathway with potential to deliver safer chronic therapies and to expand into treatment of cardiovascular disease. The pathway is of interest because metabolism of arachidonic acid (AA[a]) produces multiple mediators of inflammation including prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs). Platelet activating factor (PAF), another inflammatory mediator, can be formed from the lysophospholipid that is produced in the cleavage of membrane phospholipids by cPLA$_2$α to release AA.[1–3] Each of these mediators has been implicated in a variety of disease states. Nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors block the conversion of AA to PGs, and extensive clinical trials have confirmed that PGs are proinflammatory and potentiate pain.[4] LTB_4 contributes to inflammation by both recruiting and activating leukocytes, while cysteinyl leukotrienes (LTC_4, D_4, and E_4) promote edema by increasing vascular permeability and permitting leakage of plasma to the extravascular space.[5] 5-Lipoxygenase inhibition and LTD_4 receptor antagonists are both effective in animal models of pain.[6] Thus, there may be added benefit in inhibiting both PGs and LTs in the treatment of inflammation and pain. PAF receptor antagonists have not been successful in the clinic, but genetically altered mice either overexpressing or deficient in the PAF receptor do support a role for PAF in inflammation and pain.[7,8]

The key step in the biosynthesis of each of these potent mediators is the selective release of AA from glycerophospholipids. Cytosolic phospholipase A$_2$α (cPLA$_2$α, a group IVA phospholipase) is exceptionally well validated[3,9,10] to be the source of the AA coupled to the synthesis of the above-mentioned inflammatory mediators. The generation of gene deletion mice[10,11] has proven that cPLA$_2$α plays not only a central role in the AA pathway but in a broad range of disease states. These gene deletion mice are generally healthy and are also resistant to numerous inflammatory disease models including collagen induced arthritis,[12] ova induced model of anaphylaxis,[3] acid or sepsis induced adult respiratory distress syndrome (ARDS),[13] reperfusion injury in a model of middle cerebral artery occlusion,[14] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced model of Parkinson's disease,[15] polyp formation in APC (adenoma polyposis carcinoma) mice[16,17] and are resistant to experimental autoimmune encephalomyelitis (EAE), a model of human multiple sclerosis.[18] Clearly cPLA$_2$α represents a target for pharmaceutical intervention with the potential to yield therapeutics useful in a broad range of disease states.

The search for well-behaved cPLA$_2$α inhibitors began when the enzyme was first characterized nearly 2 decades ago. This

* To whom correspondence should be addressed. Phone: 617-665-5603. Fax: 617-665-5685. E-mail: jmckew@wyeth.com.
† Department of Chemical and Screening Sciences.
‡ Department of Inflammation.
# Department of Chemical and Pharmaceutical Development.
§ Department of Drug Safety and Metabolism.
∇ Mount Sinai Medical Center.

[a] Abbreviations: cPLA$_2$α, cytosolic phospholipase A$_2$ α; AA, arachidonic acid; PGs, prostaglandins; TXs, thromboxanes; LTs, leukotrienes; PAF, platelet activating factor; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; LTC_4, D_4, and E_4, cysteinyl leukotrienes; ARDS, adult respiratory distress syndrome; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; APC, adenoma polyposis carcinoma; EAE, experimental autoimmune encephalomyelitis; GLU, 7-hydroxycoumarinyl-γ-linolenate; A23187, a calcium ionophore; COX-1, cyclooxygenase-1; 5-LO, 5-lipoxygenase; ITC, isothermal titration calorimetry; PAPC, 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; PAPE, 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphoethanolamine; sPLA$_2$, type II secreted phospholipase A$_2$; TMPD, *N*,*N*,*N*′,*N*′-tetramethylbenzene-1,4-diamine; *F*, oral bioavailability; CPE carrageenan paw edema; CIA, collagen-induced arthritis; AIA, adjuvant-induced arthritis; AHR, acute hyperresponsiveness; LAR, late asthmatic response; FT-ICR, Fourier transform ion cyclotron resonance; ESI, electrospray ionization.

10.1021/jm701467e CCC: $40.75 © 2008 American Chemical Society
Published on Web 05/23/2008

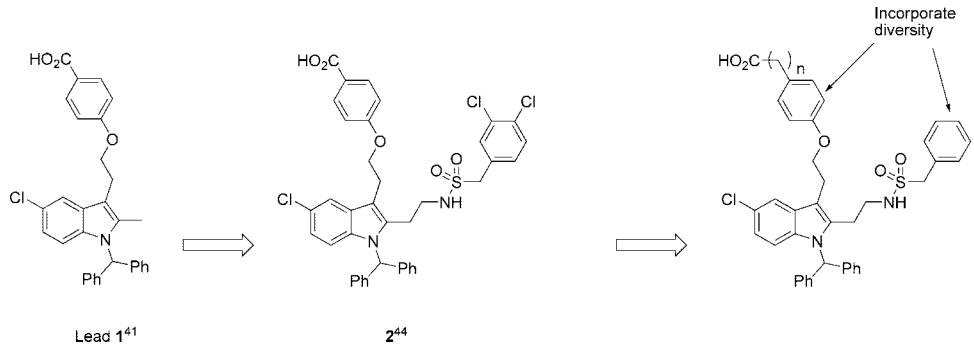


Figure 1. Wyeth's indole $cPLA_2\alpha$ inhibitors.

effort has produced compounds as distinct as electrophilic ketones,[19–24] natural products that inhibit $cPLA_2\alpha$,[25,26] and compounds that are purported to have dual $cPLA_2\alpha$ and $sPLA_2$ activity.[27] Pyrimidone inhibitors from Elan,[28] dicarboxylic acids from the Lehr group,[29–31] pyrrolidine-based inhibitors from Shionogi,[32–34] propane-2-ones from Astra Zeneca,[35] tricarbonyl inhibitors from the Dennis laboratory,[21] and the oxamide-based inhibitors from Kokotos[36,37] have been reported. Synthetic inhibitors of phopholipases have been reviewed recently.[38–40]

$cPLA_2\alpha$ assays are complicated in that $cPLA_2\alpha$ is a soluble enzyme that cleaves its phospholipid substrate at the membrane/water interface, and thus, Michaelis–Menten kinetics do not apply. The initial substrate-binding step includes the binding of the enzyme to the membrane surface and then the subsequent binding of an individual phospholipid at the active site. Therefore, the rate of reaction is dependent on the equilibrium between membrane-bound and free enzyme, substrate accessibility and replenishment, and the kinetics of the catalytic steps. In many assay systems, compounds interfering with any of these parameters score as inhibitors. We have validated an assay paradigm[41] that relies on a 7-hydroxycoumarinyl-γ-linolenate (GLU) micelle assay that allows micellar presentation of the inhibitor and substrate to the enzyme. The high lipid content in this assay selects against inhibitors that would act as inhibitors by altering the membrane surface. This assay is followed by a physiologically relevant rat whole blood assay. Stimulation of rat whole blood with A23187, a calcium ionophore, reproducibly leads to production of thomboxane A_2 that is downstream of both $cPLA_2\alpha$ and cyclooxygenase-1 (COX-1). This assay is stringent in that the blood contains both serum proteins that can bind and sequester inhibitor and a high lipid content relative to standard cellular assays. Since NSAIDS, COX-2 inhibitors, and 5-lipoxygenase (5-LO) inhibitors are all active in whole blood assays at the plasma concentrations observed in humans at clinical doses,[42,43] this assay is critical to the development of SAR and to the identification of compounds for further characterization. Finally, evidence of direct binding to target and detailed thermodynamics of binding can also be generated using isothermal titration calorimetry.[44] At Wyeth we have used these assays to develop a series of potent and selective $cPLA_2\alpha$ inhibitors.[41,44,45] When representatives of many of the classes of inhibitors mentioned above are tested under these stringent assays used to develop Wyeth's inhibitors, they have limited activity.[44] The pyrrolidine inhibitor from Shionogi is the only compound to display activity in a stringent isolated enzyme assay and in whole blood assays; however, physicochemical properties limit its activity in vivo. The oxamide described by Kokotos has been shown to have an antihyperalgesia effect with intraperitoneal and intrathecal administration[46,47] but has not been able to show the broad spectrum of activity one would expect from a potent $cPLA_2\alpha$ inhibitor.

This report details the optimization of the C3 acid linker and the nature of the sulfonamide group in the indole based series of inhibitors shown in Figure 1 and provides data on **111** (efipladib), Wyeth's second clinical candidate, and **121** (WAY-196025), a compound undergoing preclinical evaluation. These two compounds demonstrate increased potency over **2** (Ecopladib),[44] reduced clearance in vivo and efficacy in the broad range of in vivo models one would expect for compounds that inhibit $cPLA_2\alpha$.

Chemistry

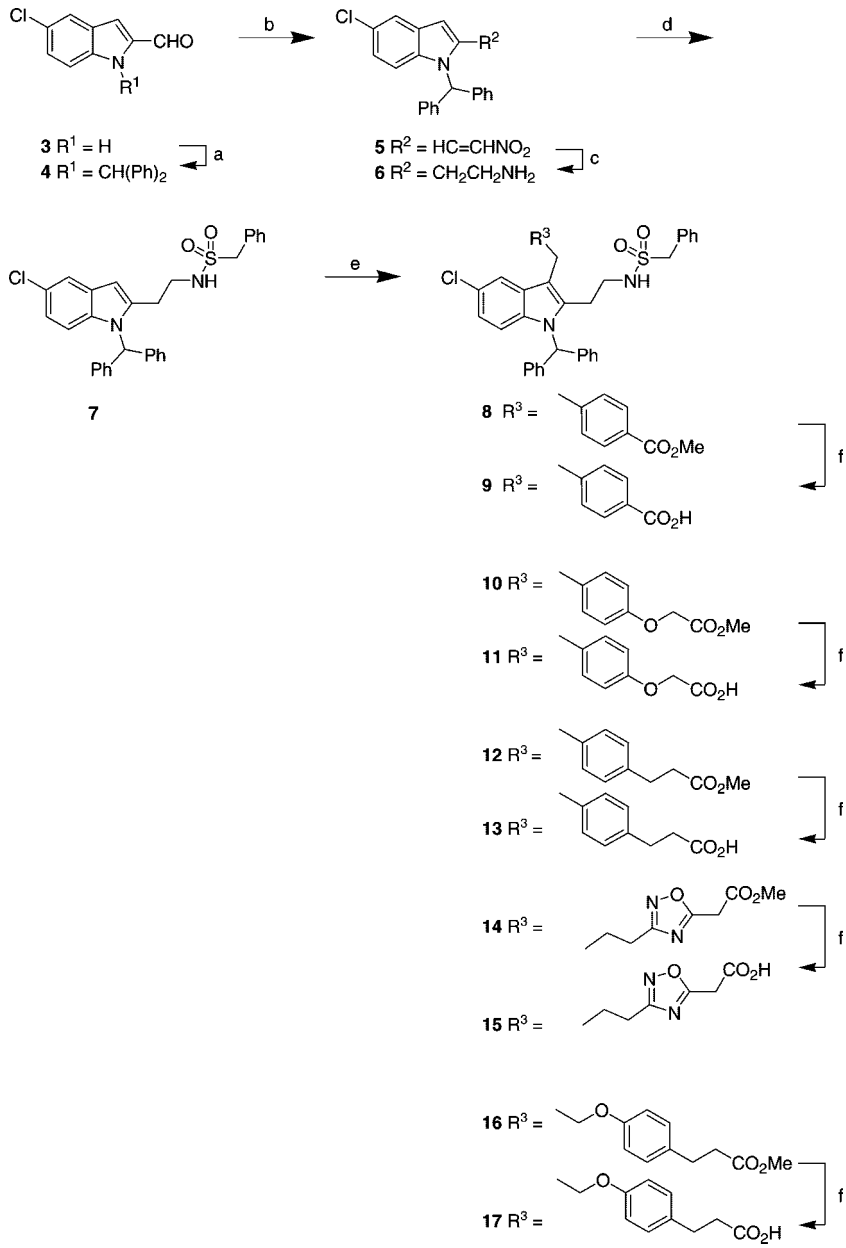
The observation[41] that more potent $cPLA_2\alpha$ inhibitors could be achieved by varying the linker between the indole ring and the benzoic acid suggested a re-examination of this part of the molecule once the third part of the pharmacophore, the C2 sulfonamide,[44] had been established. The synthetic approach that was utilized was to build on our earlier synthesis[44] and to install the C3 portion, and the required diversity, via reductive alkylation[48,49] as the penultimate step. This approach was successful for a number of analogues resulting from reaction of both aryl- and alkylaldehydes, as shown in Scheme 1. We observed side reactions, including loss of the benzhydryl group under the conditions of the reductive alkylation reaction, as well as cyclization of the sulfonamide nitrogen onto the intermediate indolium ion before it could be reduced. The formation of these undesired byproduct prompted us to explore other routes to vary the C3 position.

In order to increase the yield and the versatility of the synthesis, an approach in which the C3 group was installed earlier in the synthesis and generally gave higher yields was employed. The C3 group was added at the C2 methyl stage, (e.g., compound **18** in Scheme 2), and then the C2 methyl substituent was elaborated to the sulfonamide using previously established chemistry.[44] This approach provided the all carbon linked analogue **24**.

The installation of the sulfone linker utilized a similar approach, except the reductive alkylation was performed on the known C2 alcohol **25**[50] as depicted in Scheme 3. The alcohol was first protected as the tBDPS ether, which survived the conditions used to install the C3 linker. The C2 group was then elaborated by deprotection to the alcohol, activation as the mesylate, displacement by azide, reduction to the amine, and then sulfonylation to produce **35** after hydrolysis of the C3 methyl ester.

Another synthetic approach was used to synthesize C3 linkers with sulfone propionate functionality. The known alcohol **36**,[44] Scheme 4, was activated as the bromide and then displaced with

Scheme 1. Late Stage Introduction of C3 Linker[a]



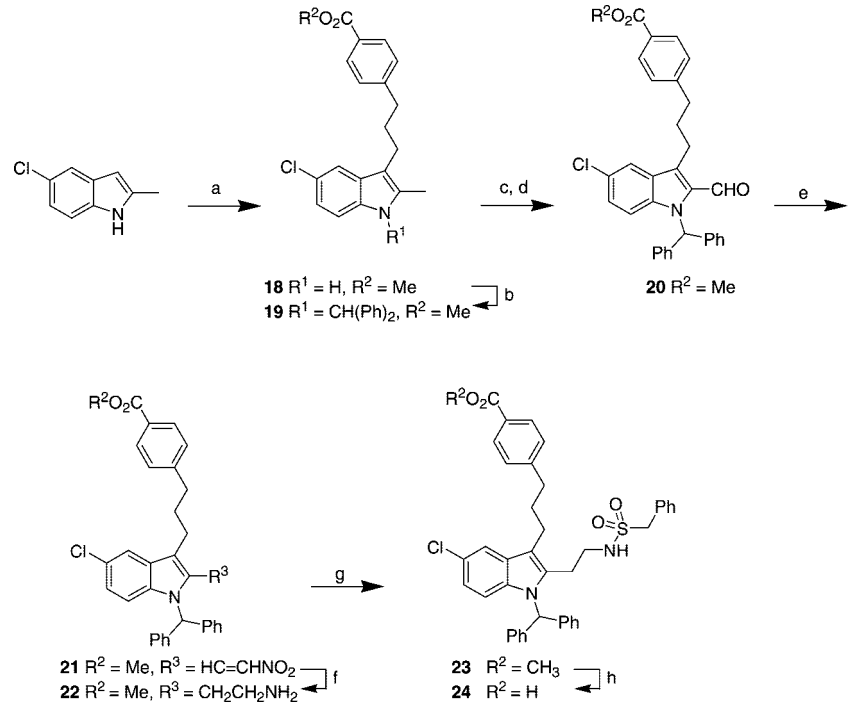
[a] (a) NaH, DMF, $BrCH(Ph)_2$; (b) CH_3NO_2, NH_4OAc, reflux; (c) Zn(Hg) amalgam, HCl, THF; (d) $NaHCO_3$, $PhCH_2SO_2Cl$, CH_2Cl_2; (e) R^3CHO or $R^3CH(OEt)_2$, TFA, Et_3SiH; (f) NaOH, THF, MeOH.

the desired thiol nucleophile. Thioether **38** was then oxidized with TPAP/NMO to the sulfone, and then the C2 substituent was elaborated to the amine as shown earlier. The amine was then sulfonylated and the ester hydrolyzed to yield the desired **45**.

The synthesis of amine-linked analogues made use of the same versatile intermediate **36**, as shown in Scheme 5. In this case, the alcohol was oxidized under Swern conditions and the resulting aldehyde was treated with a primary or secondary amine under reductive amination conditions to install the benzoate. Both of these intermediates were then elaborated at C2 to the amine as described above, then sulfonylated, and the C3 ester was hydrolyzed to yield the desired acids **58** and **60**.

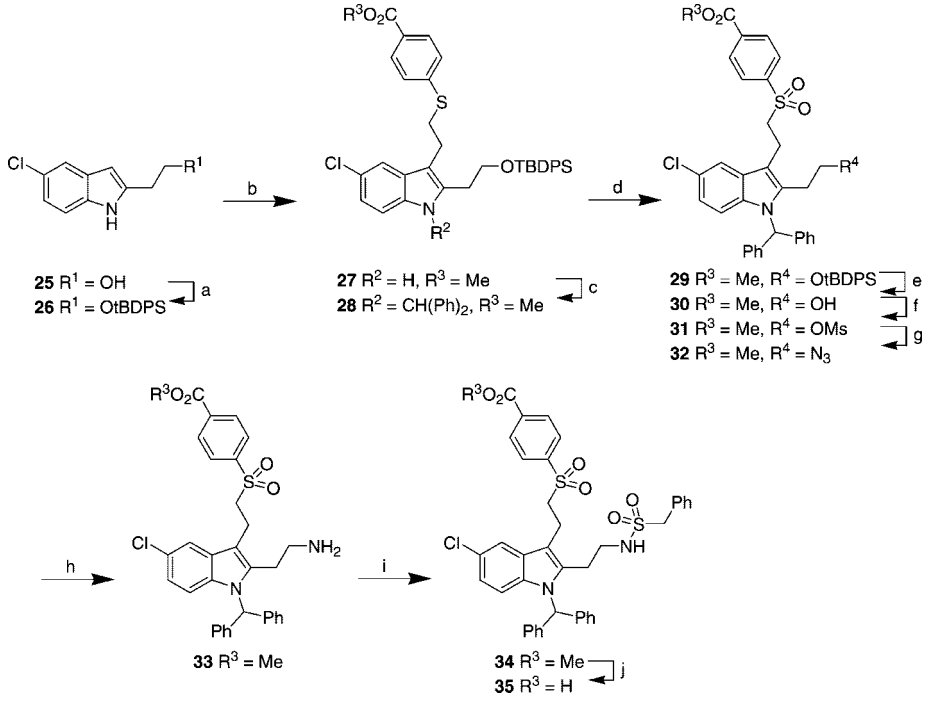
We next varied the substituent on the sulfonamide portion of the molecule. Earlier SAR[44] had shown that a benzyl substituent was much more potent than unsubstituted phenyl and that substitution in this ring could have a dramatic impact on in vivo clearance in rats. The synthesis of the analogues was accomplished by simply coupling the amino ester **79** (Scheme 8) with sulfonyl chlorides under Schotten−Baumann conditions. This approach successfully provided much diversity at this position with the C3 oxygen linked series. More challenging was the fact that only a handful of substituted phenylmethane sulfonyl chlorides were commercially available at the time of this work. We used a variety of literature methods[51] to synthesize reagents (see Scheme 6) and modified conditions to generate more difficult to synthesize compounds such as the 2,6-disubstituted reagents shown in Scheme 7. It is has been reported[52] that under standard conditions to synthesize sulfonyl chlorides from benzyl halides, extrusion of SO_2 occurs, returning starting halide and significantly lowering the yield of the desired sulfonyl chloride. Therefore, reaction conditions were modified

Scheme 2. Synthesis of a Propyl C3 Linker[a]



[a] (a) Methyl 4-(2-formylethyl)benzoate, TFA, Et_3SiH; (b) NaH, DMF, $BrCH(Ph)_2$; (c) NBS, benzoyl peroxide, CCl_4; (d) Ag_2CO_3, H_2O, acetone; (e) CH_3NO_2, NH_4OAc, reflux; (f) Zn(Hg) amalgam, HCl, THF; (g) $NaHCO_3$, $PhCH_2SO_2Cl$, CH_2Cl_2; (h) NaOH, THF, MeOH.

Scheme 3. Synthesis of C3 Sulfone Benzoate Linker[a]



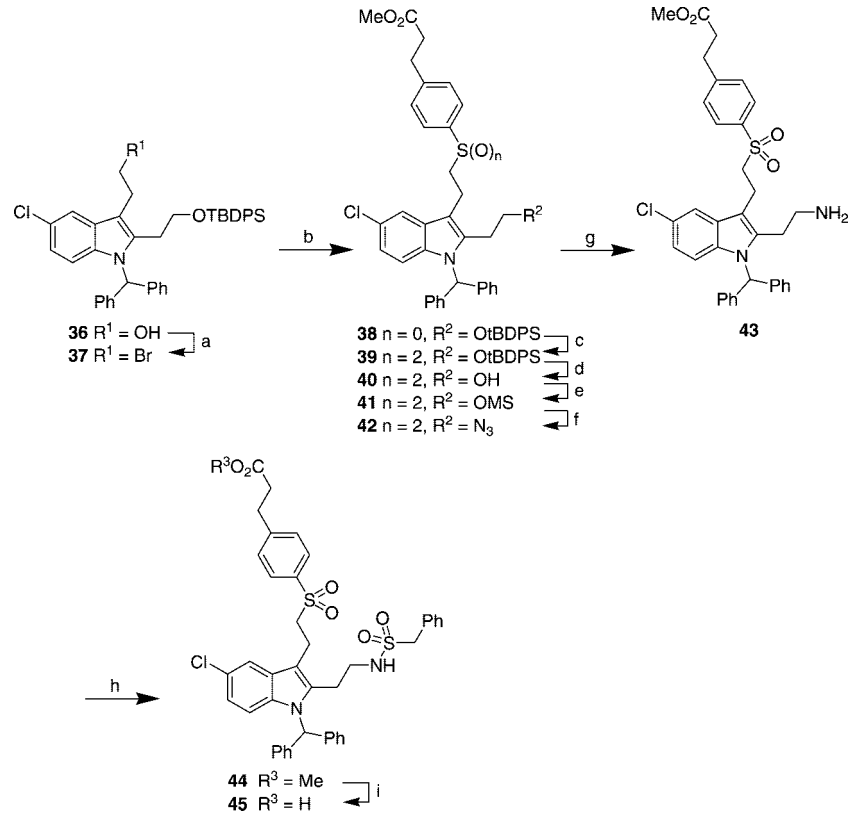
[a] (a) tBDPSCl, imidazole, DMF; (b) methyl 4-[(2-oxoethyl)thio]benzoate,[41] TFA, Et_3SiH; (c) NaH, DMF, $BrCH(Ph)_2$; (d) NMO, TPAP; (e) TBAF, THF; (f) MsCl, Et_3N; (g) NaN_3, DMF, 60 °C; (h) PPh_3, H_2O, THF; (i) $NaHCO_3$, $PhCH_2SO_2Cl$, CH_2Cl_2; (j) NaOH, THF, MeOH.

as shown in Scheme 7 to avoid this. Specifically, we found that if the sodium salt of the sulfonic acid, e.g., **74**, is protonated with gaseous HCl before treatment with oxalyl chloride, the yield of sulfonyl chloride **77** increases from <10% without HCl treatment to reproducibly ~90%. This method was also applicable to monosubstituted benzyl halides. The reaction thus performed was amenable to scale-up.

With these sulfonyl chloride reagents in hand, variations to the sulfonamide were quickly explored using the route shown in Scheme 8 for the C3 ether linked amine.

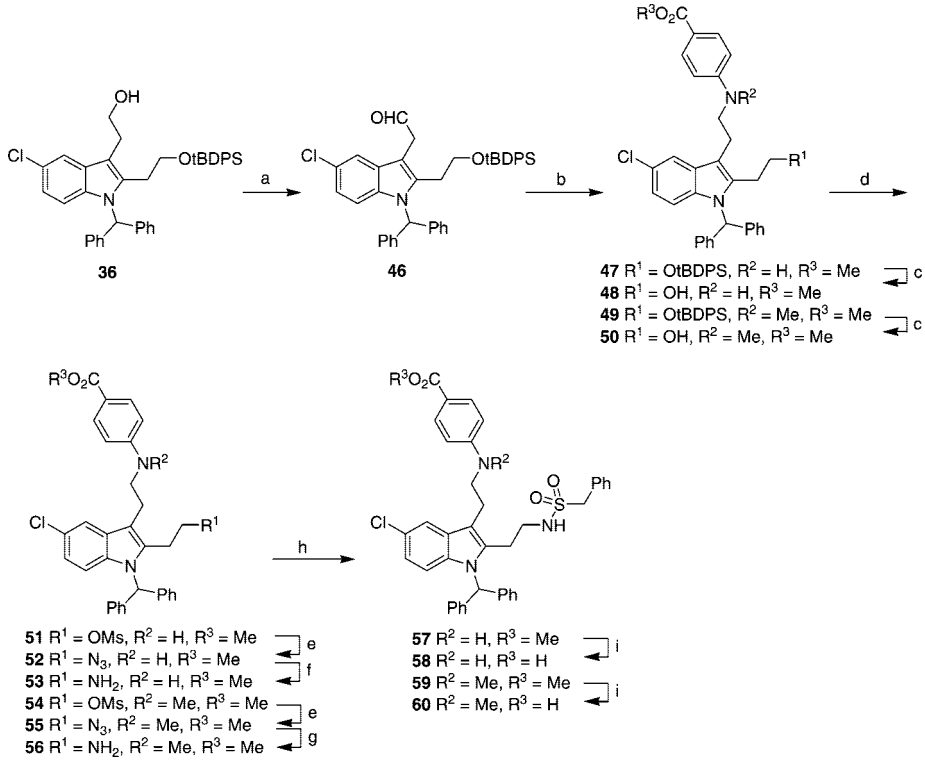
This same approach was used to make sulfonamide analogues with C3 methylene and sulfone linkers shown in Scheme 9. Sulfone propionates were made as shown in Scheme 10 from the amino methyl ester previously described

Scheme 4. Synthesis of C3 Sulfone Propionate Linked Analogues[a]



[a] (a) DPPP, CBr_4; (b) K_2CO_3, methyl-3-(4-mercaptophenyl)propionate, DMF; (c) NMO, TPAP, ACN; (d) TBAF, THF, H_2O; (e) MsCl, Et_3N, CH_2Cl_2; (f) NaN_3, DMF, 60 °C; (g) PPh_3, THF, H_2O; (h) $PhCH_2SO_2Cl$, $NaHCO_3$, CH_2Cl_2; (i) NaOH, THF, H_2O.

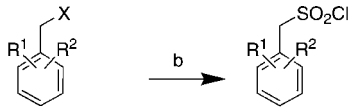
Scheme 5. Synthesis of C3 Amine Linked Analogues[a]



[a] (a) oxalyl chloride, DMSO, DIPEA; (b) $NaBH(OAc)_3$, methyl 4-aminobenzoate for **47** and methyl 4-(methylamino)benzoate for **49**; (c) TBAF, THF, HOAc; (d) MsCl, NEt_3; (e) NaN_3; (f) PPh_3,THF, H_2O; (g) H_2, Pd/C; (h) $PhCH_2SO_2Cl$, $NaHCO_3$, CH_2Cl_2; (i) NaOH, THF, MeOH.

(**43** in Scheme 4) or from the amino ethyl ester synthesized using similar chemistry. The chemistry described herein allowed the synthesis of multiple analogues and allowed a full SAR to be developed. The chemistry was also versatile

Scheme 6. Synthesis of Novel Sulfonyl Chlorides[a]



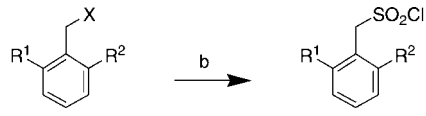
61 R^1 = 2-CN, R^2 = H, X = Br
62 R^1 = 2-CN, R^2 = H, X = SO_3H
63 R^1 = 3-$CONH_2$, R^2 = H, X = Br
64 R^1 = 3-$CONH_2$, R^2 = H, X = SO_3H
65 R^1 = 4-CN, R^2 = H, X = Br
66 R^1 = 4-CN, R^2 = H, X = SO_3H
67 R^1, R^2 = C_4H_4, X = Br
68 R^1, R^2 = C_4H_4, X = SO_3H

a

69 R^1 = 2-CN, R^2 = H
70 R^1 = 3-CN, R^2 = H
71 R^1 = 4-CN, R^2 = H
72 R^1, R^2 = C_4H_4

[a] (a) Na_2SO_3, EtOH; (b) $SOCl_2$, DMF.

Scheme 7. High Yielding Synthesis of Hindered Sulfonyl Chlorides[a]



73 R^1, R^2 = CH_3, X = Br
74 R^1, R^2 = CH_3, X = SO_3H
75 R^1, R^2 = F, X = Br
76 R^1, R^2 = F, X = SO_3H

a

77 R^1, R^2 = CH_3
78 R^1, R^2 = F

[a] (a) (i) Na_2SO_3, TBAI, H_2O; (ii) HCl (g), CH_3OH; (b) oxalyl chloride, THF.

enough to allow the synthesis of key compounds on gram scale for further characterization.

Results and Discussion

Previous SAR had elucidated that a three atom linker to a benzoic acid at the C3 position of these indole $cPLA_2\alpha$ inhibitors was essential for well-behaved inhibitors.[41] Subsequently, extension at C2 through an ethyl bridge to a benzyl sulfonamide[44] was determined to be essential for nanomolar potency in both isolated enzyme and whole blood assays. Once this level of potency was achieved, the C3 linker was revisited. Table 1 displays variations to the C3 substituent. First, shortening the benzoic acid linker, or sliding the benzene ring closer to the indole while maintaining the distance, as in **9**−**13**, dramatically reduced potency when compared to **141**.[44] When the benzene was replaced with an oxadiazole, **15**, potency was again significantly reduced. When the benzoic acid was extended to a propionic acid, **17**, potency was maintained. This SAR trend had also been observed in compounds that were significantly less potent. When the linker was modified to the all carbon linker **24** or the sulfone linker **35**, potency in both assays increased significantly. Sulfone propionate **45** was the most potent compound in the rat whole blood assay with a low nanomolar IC_{50}. When a secondary or tertiary amine linker, **58** or **60**, was examined, potency dropped off dramatically. The compounds that were most promising were the ether, methylene, and sulfone benzoates and propionates. It is difficult to speculate as to what property caused the increase in potency in this series because effects on benzoic acid pK_a or hydrogen bond donor/acceptor properties do not correlate with the observed potency changes. This quick re-examination of the C3 linker gave a defined group of very potent compounds to further optimize.

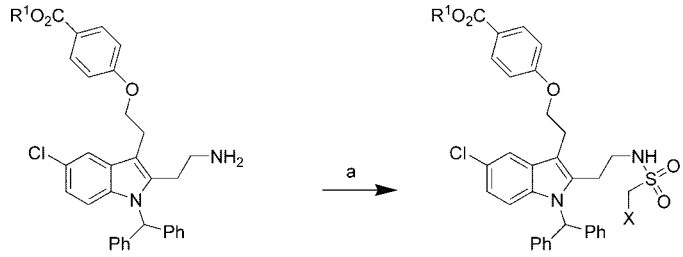
Another region of the pharmacophore that was ripe for further optimization was the benzyl sulfonamide. Previous efforts[44] had shown this region to be very important in both enabling nanomolar inhibitors and providing a platform for substitutions that would attenuate the high clearance seen with **141**. Previously, halogens had been used to probe space around this ring; a broader scan of allowed functionality is shown in Table 2. Both the nitro group and cyano group were allowed at all positions. Substitution of the phenyl ring by the three pyridyl regioisomers also resulted in very potent compounds. This substitution allows a decrease of ∼1.5 log units of clogP and indicates the feasibility of using this region to modify physicochemical properties. Other interesting analogues include the cyclohexyl and the napthyl analogues, both of which were quite potent. The ability to substitute around all positions of the phenyl ring, incorporate polarity or increased size renders this sulfonamide region a versatile part of the pharmacophore.

With the knowledge gained from varying the linker to the acid functionality and a broader understanding of the allowed functionality at the sulfonamide region, it seemed prudent to explore variations at the sulfonamide with some of the more potent linkers. These data are summarized in Table 3. Compounds that had increased potency over **141** and **2** with lower in vivo clearance values were desired. All four potent linkers were examined with multiple sulfonamide substitution patterns, and assay data and rat clearance (CL) after iv administration are reported in Table 3. From the unsubstituted analogues, only methylene linker **24** is potent and cleared slowly in vivo. The 3,4-dichloro substitution remarkably lowered the clearance in **2**, **111**, **113**, and **138** when compared to their unsubstituted counterparts while also maintaining potency. In fact, **111** showed the pattern sought, a low nanomolar inhibitor that was cleared quite slowly. More focus was given to 2-substition and 2,6-disubstitution of the sulfonamide. The 2-chloro analogues were all quite potent, but unfortunately all of these analogues, with the exception of **115**, showed rapid clearance. The 2-methyl analogues were also potent and typically had reduced clearance when compared to the 2-chloro analogues. The 2,6-dimethyl substitution also yielded very potent compounds, now with acceptable clearance (<20 (mL/min)/kg). In fact **121** is significantly more potent while being cleared much more slowly than **2**. The 2,6-difluoro substituents were also explored with each linker and also yielded very potent analogues. Unfortunately, most of these compounds were also cleared rapidly and were unsuitable for further in vivo studies. The trends seen in this table were that 2- and 2,6-substitution patterns generally resulted in more potent compounds. The 2,6-dimethyl substitution increased potency and resulted in compounds with attenuated clearance, whereas the 3,4-dichloro analogues maintained potency but also had reduced clearance. Within a given series, the clearance was dependent on the linker; the methylene linkers were cleared more slowly, while the sulfone benzoates and propionates were cleared much more rapidly. Several examples of oxygen and methylene linked analogues were chosen for further in vitro and in vivo validation.

As noted earlier, the GLU micelle assay can filter out compounds that are presented as false positives by disrupting the membrane/water interface without forming 1:1 interactions with $cPLA_2\alpha$. We note that at the GLU micelle IC_{50} values listed in Table 3, which vary from 0.15 to 0.004 μM, there are >7000 to >250 000 molecules of triton or lipid for every molecule of inhibitor. Therefore, we felt it was likely that these molecules bind directly to $cPLA_2\alpha$ and do not affect the membrane surface.

Since **111** and **121** combined the properties of high potency and low clearance, these compounds were characterized more

Scheme 8. Sulfonamide Analogues with a C3 Ether Linkage[a]



79

80 X = 2-NO_2Ph, R^1 = CH_3 — b
81 X = 2-NO_2Ph, R^1 = H — b

82 X = 3-NO_2Ph, R^1 = CH_3 — b
83 X = 3-NO_2Ph, R^1 = H — b

84 X = 4-NO_2Ph, R^1 = CH_3 — b
85 X = 4-NO_2Ph, R^1 = H — b

86 X = 2-CNPh, R^1 = CH_3 — b
87 X = 2-CNPh, R^1 = H — b

88 X = 3-CNPh, R^1 = CH_3 — b
89 X = 3-CNPh, R^1 = H — b

90 X = 4-CNPh, R^1 = CH_3 — b
91 X = 4-CNPh, R^1 = H — b

92 X = 2-Pyridyl, R^1 = CH_3 — b
93 X = 2-Pyridyl, R^1 = H — b

94 X = 3-Pyridyl, R^1 = CH_3
95 X = 3-Pyridyl, R^1 = H — b

96 X = 4-Pyridyl, R^1 = CH_3 — b
97 X = 4-Pyridyl, R^1 = H — b

98 X = Cyclohexyl, R^1 = CH_3 — b
99 X = Cyclohexyl, R^1 = H — b

100 X = 2-Naphthyl, R^1 = CH_3 — b
101 X = 2-Naphthyl, R^1 = H — b

102 X = 2-ClPh, R^1 = CH_3 — b
103 X = 2-ClPh, R^1 = H — b

104 X = 2-MePh, R^1 = CH_3 — b
105 X = 2-MePh, R^1 = H — b

106 X = 2,6-MePh, R^1 = CH_3 — b
107 X = 2,6-MePh, R^1 = H — b

108 X = 2,6-FPh, R^1 = CH_3 — b
109 X = 2,6-FPh, R^1 = H — b

[a] (a) RSO_2Cl, $NaHCO_3$, CH_2Cl_2; (b) NaOH, THF, MeOH.

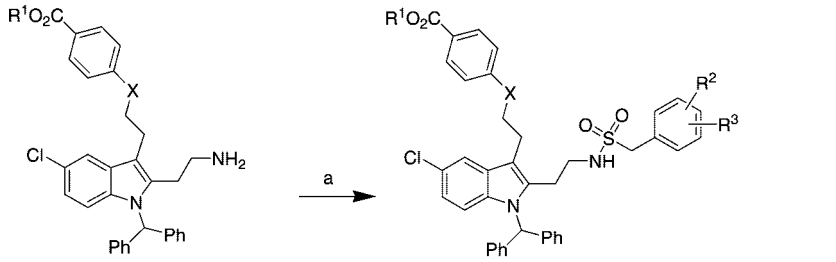
carefully. After confirmation that both inhibitors were reversible inhibitors in the GLU micelle assay, their binding properties were measured by isothermal titration calorimetry (ITC) using triton micelles analogous to those used in the GLU micelle assay.[53] In ITC, cPLA$_2\alpha$ in the presence of micelles is titrated with inhibitor also in the presence of micelles, and the heat released with each equal addition of inhibitor is measured until cPLA$_2\alpha$ is saturated with compound. No detectable heat was generated when inhibitors were titrated against assay buffer alone. The binding to cPLA$_2\alpha$ is exothermic for both compounds, and the isotherm fits well with a single site model, indicating that one molecule of each inhibitor interacts with one molecule of cPLA$_2\alpha$. The K_d for **111** was determined to be 0.067 and 0.013 μM for **121**. These values agree with the IC_{50} values from the GLU micelle assays, which are 0.04 and 0.01 μM respectively.

Two isoforms of cPLA$_2\alpha$ were initially identified, cPLA$_2\beta$ and cPLA$_2\gamma$, while more recently, three additional isoforms closely related to cPLA$_2\beta$ were identified.[54] To assess selectivity, **111** and **121** were assayed for their ability to inhibit cPLA$_2\beta$ and γ, which are ~35% identical in the catalytic domains. By use of PAPC (1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine) liposomes to assess activity, **111** and **121** both showed greater than 90% inhibition of cPLA$_2\alpha$ at a concentration of 0.020 μM but no inhibition with cPLA$_2\beta$, and cPLA$_2\gamma$ at concentrations as high as 0.5 μM. Similarly, by use of PAPE (1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphoethanolamine) liposome assays to monitor inhibition of type II secreted phospholipase A_2 (sPLA$_2$), both compounds inhibited cPLA$_2\alpha$ in this assay with IC_{50} < 0.010 μM but did not inhibit sPLA$_2$ at 0.5 μM.

MC-9 cells are a murine mast cell line that can be stimulated through the IgE receptor to activate release of arachidonic acid from the cellular membrane[44] resulting in generation of prostaglandins by the COX-1 pathway and leukotrienes by the 5-LO pathway. As expected, the 5-LO inhibitor zileuton[55,56] (*N*-[1-(1-benzothien-2-yl)ethyl]-*N*-hydroxyurea) selectively inhibits LT production in this assay but does not effect PG production. The COX-1 dependence of the assay was confirmed using SC-560[57] (5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazole) and celecoxib,[58](4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide), which are structurally related but highly selective for COX-1 and COX-2, respectively (see Table 4). The COX-1-dependent PG synthesis can also be initiated by bypassing cPLA$_2\alpha$ with the addition of exogenous AA directly to the cells. In this case, NSAIDs such as naproxen ((2*S*)-2-(6-methoxy-2-naphthyl)propanoic acid) and COX-1 selective inhibitors will still inhibit PG production, but a selective cPLA$_2\alpha$ inhibitor should not. When **111** and **121** were tested in this assay, they were found to inhibit LT and PG production with similar IC_{50} values for each pathway, suggesting inhibition of AA release. When cPLA$_2\alpha$ was bypassed by the addition of exogenous AA, the inhibitors did not affect PGF$_2\alpha$ production, indicating that they do not inhibit COX-1.

111 was also tested in a COX-2 dependent PGE_2[59] assay using A549 cells. In this assay, A549 cells are stimulated overnight with IL-1B to induce COX-2 expression, and the medium is removed and replaced with medium containing either inhibitor alone or inhibitor plus exogenous AA. Celecoxib inhibits PGE_2 production in the presence or absence of AA. In contrast, **111** inhibited PGE_2 production by >95% at 0.040 μM in the absence

Scheme 9. Sulfonamide Analogues with a C3 Methylene and Sulfone Linkers[a]



22 X = CH_2
33 X = SO_2

110 X = CH_2, R^1 = CH_3, R^2 = 3-Cl, R^3 = 4-Cl
111 X = CH_2, R^1 = H, R^2 = 3-Cl, R^3 = 4-Cl

112 X = SO_2, R^1 = CH_3, R^2 = 3-Cl, R^3 = 4-Cl
113 X = SO_2, R^1 = H, R^2 = 3-Cl, R^3 = 4-Cl

114 X = CH_2, R^1 = CH_3, R^2 = 2-Cl, R^3 = H
115 X = CH_2, R^1 = H, R^2 = 2-Cl, R^3 = H

116 X = SO_2, R^1 = CH_3, R^2 = 2-Cl, R^3 = H
117 X = SO_2, R^1 = H, R^2 = 2-Cl, R^3 = H

118 X = CH_2, R^1 = CH_3, R^2 = 2-Me, R^3 = H
119 X = CH_2, R^1 = H, R^2 = 2-Me, R^3 = H

120 X = CH_2, R^1 = CH_3, R^2 = 2-CH_3, R^3 = 6-CH_3
121 X = CH_2, R^1 = H, R^2 = 2-CH_3, R^3 = 6-CH_3

122 X = SO_2, R^1 = CH_3, R2 = 2-CH_3, R^3 = 6-CH_3
123 X = SO_2, R^1 = H, R^2 = 2-CH_3, R^3 = 6-CH_3

124 X = CH_2, R^1 = CH_3, R^2 = 2-F, R^3 = 6-F
125 X = CH_2, R^1 = H, R^2 = 2-F, R^3 = 6-F

126 X = SO_2, R^1 = CH_3, R^2 = 2-F, R^3 = 6-F
127 X = SO_2, R^1 = H, R^2 = 2-F, R^3 = 6-F

b

[a] (a) RSO_2Cl, $NaHCO_3$, CH_2Cl_2; (b) NaOH, THF, MeOH.

of exogenous arachidonate but was inactive at 1 μM when cPLA$_2$α was bypassed with exogenous AA. This assay adds additional evidence that **111** acts through the inhibition of cPLA$_2$α in cells.

Finally, **111** and **121** were also assayed for their ability to inhibit COX-1 and 2 in microsomes in a colorimetric COX assay (Cayman Chemical) where the oxidation of *N*,*N*,*N*′,*N*′-tetramethylbenzene-1,4-diamine, TMPD, is monitored. No inhibition was observed at 100 μM.

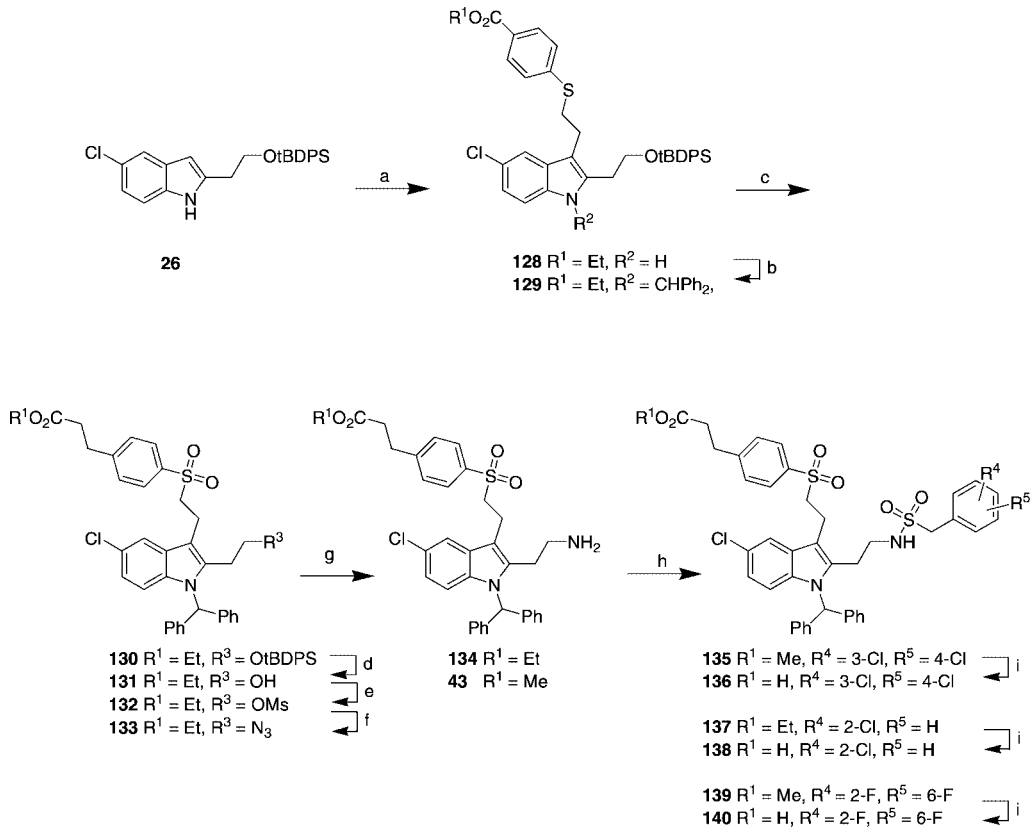
Inhibition of these inhibitors in a human whole blood (HWB) assay was also examined. The rat and human[44] whole blood assays are similar except the A23187 concentration required for consistent stimulation is 30 μM for human blood vs 5 μM for rat. In addition, we test for a broader range of AA metabolites and also monitor PAF production. The results in Table 5 indicate that these inhibitors are acting on cPLA$_2$α where they can block the initial cleavage of arachidonoyl phospholipids to generate free AA and lyso-PC, which is the precursor to PAF.

The data presented above were sufficient to convince us that these inhibitors were potent and selective inhibitors of cPLA$_2$α capable of inhibiting multiple classes of inflammatory mediators. The in vivo clearance value, presented in Table 3, shows both of these compounds to be cleared quite slowly in rats. The pharmacokinetics from oral dosing for both inhibitors were examined as a prelude to in vivo pharmacology models, and the oral bioavailability (*F*) for **111** and **121** in rats was 6% and 4%, respectively. Despite this low bioavailability, the plasma levels from reasonable po doses exceeded the rat whole blood IC_{50} values, and therefore examination of the in vivo efficacy of these compounds was warranted. These compounds were compared to **2**, which has slightly better bioavailability but lower potency and higher clearance. In estimating in vivo potential, we found oral exposure following 25 mg/kg po dosing divided by the IC_{50} in rat whole blood to be informative for prioritizing compounds. These AUC/IC_{50} values are listed in Table 6.

The strategy for evaluating these compounds in vivo was to explore standard inflammation and asthma models in which AA metabolites play a central role. COX-2 selective inhibitors and NSAIDs have been characterized previously in short-term models, including the rat air pouch model[57,60,61] and the carrageenan paw edema (CPE) model.[62] In the air pouch model, carrageenan is injected into a preformed air pouch 2 h after po administration of drug. Air pouch contents are then removed 6 h later, and the amount of PGE_2 produced is quantitated. In developing the assay internally, we demonstrated that celecoxib administered at 2 mg/kg ip inhibited ∼90% of the PGE_2 production. For each of the cPLA$_2$α inhibitors tested, the maximum inhibition of PGE_2 was >90%. As shown in Table 6, all three compounds were active, with **121** the most potent. The ED_{50} for **2** was more variable, but when tested head to head with **121**, in multiple experiments at 5 mg/kg, **121** gave >50% inhibition whereas **2** showed <10%. This is consistent with the predictions of relative potency from the AUC/IC_{50} values.

The rat CPE model has been used extensively to evaluate NSAIDS and selective COX-2 inhibitors, and activity in this model correlates well with clinical efficacy in man.[63] In this model, compound is administered 2 h before subplantar injection of carrageenan and the inhibition of swelling over the next 3 h is measured. The maximum inhibition effect observed is ∼50%

Scheme 10. Sulfonamide Analogues with Sulfone Propionate Linkers[a]



[a] (a) TFA, Et_3SiH, ethyl 4-(2-oxoethyl)sulfanylpropanoate; (b) NaH, DMF, $BrCH(Ph)_2$; (c) NMO, TPAP; (d) TBAF; (e) MsCl, NEt_3; (f) NaN_3, DMF, 60° C; (g) PPh_3, H_2O, THF; (h) RSO_2Cl; $NaHCO_3$, CH_2Cl_2; (i) NaOH, THF, MeOH.

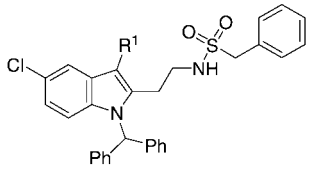
when dosed with naproxen po at a dose of ≥10 mg/kg, and the ED_{50} is defined as the dose that inhibits 25%, or half-the maximal value. Again, **121** was superior to **111** and **2** (see Table 6). The differential between **111** and **2** was less pronounced presumably because the main advantage of **111** is slower clearance, which is less important in this short-term model. In five independent experiments where **121** and celecoxib were compared at 25 mg/kg to determine the near maximum effect, the inhibition of edema was essentially identical at 34 ± 9% for **121** and 37 ± 15% for celecoxib (reported as % inhibition of edema ± SE).

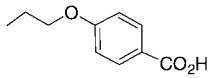
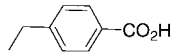
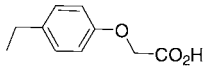
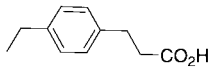
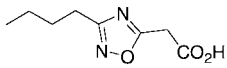
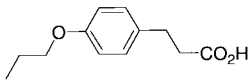
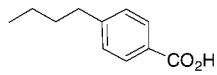
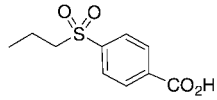
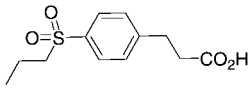
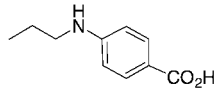
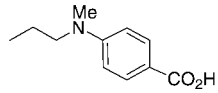
To characterize these compounds in a long-term model, **2**, **111**, and **121** were tested in the mouse collagen-induced arthritis (CIA) model, which has many immunological and pathological similarities to human rheumatoid arthritis. We had previously reported that cPLA$_2\alpha$ deficient mice were resistant to disease in this model.[12] Efficacy was assessed in a semitherapeutic dosing regimen, which involved scoring and assignment to treatment groups when 10% of the mice showed disease symptoms. All animals were scored daily in a blinded fashion for signs of disease symptoms. The data in Table 7 represent a summary of the scores in the treatment groups compared to the vehicle groups in each experiment. Both **121** and **111** (tested at a single dose level of 100 mg/kg, b.i.d.) gave a dramatic reduction in the clinical disease severity score relative to the vehicle treated group, whereas **2** with its poorer potency relative to **121** was only marginally effective. The reduction in disease score correlated with the histological assessment where each paw was assigned a numerical score for arthritis severity and the general number of joints affected. In addition, the **121** and **111** animals had a high percentage of paws with grade 0 arthritis (>80%) and no paws with grade 4 (severe) arthritis. In contrast, 17% of vehicle treated mice had a severity score of 4 and only 39% of the paws were unaffected. We were surprised that **111** outperformed **121** in this study and also in a repeat study, but plasma levels taken at the end of the experiment with time points spanning the peak and trough plasma levels showed that the exposure of **111** was significantly higher than that seen for **121**.

To further assess efficacy in long-term models predictive of clinical utility, **111** and **121** were studied in adjuvant-induced arthritis (AIA) in Lewis rats. Adjuvant arthritis was induced in Lewis rats by intradermal injection of complete Freund's adjuvant at the base of the tail. Treatment was begun at day 8 when mean clinical joint scores were 12 and continued for 11 days, and the hind paws were scored daily for clinical signs of arthritis. Treatment with celecoxib, **111**, and **121**, at doses as low as 5 mg/kg, rapidly reduced the mean clinical joint scores to levels between 0 and 1. At the completion of the 11-day experiment, the tarsal joints were collected at necropsy and prepared for histologic examination, and the arthritic lesions in each animal were evaluated in a blinded fashion. Each tarsal was assigned a numerical score for synovitis (synovitis score, 0–11, 11 is most severe) and cartilage damage[64] (Mankin score, 0–14, 14 most severe). As can be seen in Table 8, **111**, **121**, and celecoxib were efficacious with a clear, statistically significant reduction in synovitis and cartilage damage at all doses. There was no statistically significant difference between the nonvehicle treated groups.

Allergen-induced reversible airway bronchoconstriction and acute hyperresponsiveness (AHR) are two hallmark features of allergic asthma that can be examined in vivo in a sheep model of asthma. Studies performed in this animal model present strong evidence that the release of AA metabolites plays an important role in the development of late bronchial responses to antigen

Table 1. SAR from C3 Linker Variations



Compd	R^1	IC$_{50}$ (μM) GLU Micelle[a]	IC$_{50}$ (μM) RWB TXB$_2$[b]
141		0.11	0.12
9		33	>10
11		7	>10
13		2	0.9
15		>20	NT[c]
17		0.19	0.07
24		0.07	0.07
35		0.02	0.08
45		0.03	0.02
58		0.68	0.40
60		4.3	1.8

[a] Assay protocol reported previously.[41] Values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously.[41] Values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays. [c] NT = not tested.

challenge.[65] The 5-LO inhibitor zileuton blocks allergen-induced late airway responses, inflammation, and AHR[55] in this model, whereas a continuous iv infusion of the selective LTD$_4$ receptor antagonist montelukast attenuates both the early and late-phase asthmatic responses.[66,67] PAF has also been implicated in the late-phase response in this model, suggesting[68,69] that a more complete blockade of lipid mediators by a cPLA$_2$α antagonist may be beneficial. When cPLA$_2$α inhibitors **121** and **111** where dosed po b.i.d. the day before and 2 h before the time of antigen challenge, they both had a dramatic impact on the late asthmatic response (LAR) as shown in Table 9. A fourth po dose was then administered 8 h after antigen challenge. The following day AHR due to aerosolized carbachol was measured and compared to historical control values pre- and postantigen challenge. As can be seen from Table 9, both cPLA$_2$α inhibitors dramatically attenuated the late phase bronchocontriction because of allergen challenge and AHR as measured by a secondary carbachol challenge. Activity in this model shows that cPLA$_2$α inhibitors display significant efficacy in LT dependent in vivo models.

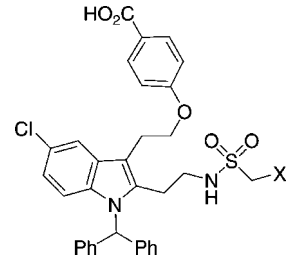
These indole cPLA$_2$α inhibitors are potent and selective in a variety of stringent assay formats in vitro and in vivo. All of the previously reported inhibitors of this target tend to be large lipophilic molecules or have electrophilic ketones or both. The potent inhibitors disclosed here also are large, but notably, increases in molecular weight in areas allowed by the pharmacophore[44] have returned substantial increases in potency. The stringent assays used to evaluate these compounds have proven to resist false positives and as such accurately reflect binding to the target. One way to examine this trend is through the concept of ligand efficiency.[70,71] The graph in Figure 2 represents on the *Y* axis the log of the IC$_{50}$ of all of the indole cPLA$_2$α inhibitors, and heavy atom count is on the *X* axis. What can be clearly seen is the trend that when molecular weight is added in an allowed part of the pharmacophore, potency is increased (along the top of the curve) and when molecular weight is added in places not allowed by the pharmacophore, potency is lost (bottom of the curve). The initial validated hits[41] are the two blue triangles with atom count of ∼36. These compounds were optimized to the three blue triangles, from bottom to top **2**, **111**, **121**. A significant increase in potency was gained from the increase in molecular weight. It can also be seen that without increasing atom count further, increases in potency could be attained. The top of the curve continues to increase beyond the highlighted compounds; however, the trade off between atom count and potency becomes less appealing.

In summary we have disclosed a group of indole cPLA$_2$α inhibitors that are potent and selective. These compounds are potent in stringent isolated enzyme assays, cell-based assays, and rat and human whole blood assays, and their binding has been further characterized using isothermal titration calorimetry. Examples from this series have been profiled in vivo in both PG and LT dependent models and have shown impressive efficacy when dosed po. These are the first cPLA$_2$α inhibitors to show PO in vivo efficacy[72] in this broad a class of in vivo models, and as such, they begin to demonstrate the therapeutic potential of cPLA$_2$α inhibitors. Clinical trials to evaluate the efficacy of **111** in humans have been initiated, and **121** continues to be profiled in preclinical models. Additional in vivo efficacy data will published shortly.

Experimental Section

Chemistry 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. Aqueous workup was performed using H_2O and brine, and organic solutions were dried with $MgSO_4$ unless otherwise noted. Proton NMR spectra were recorded on a 300 MHz Varian Gemini 2000, a 400 MHz Bruker AV-400, or a 500 MHz Bruker AV-400 using TMS (δ 0.0) as a reference. Combustion analyses were obtained using a Perkin-Elmer series II 2400 CHNS/O analyzer or by Robertson-Microlit. 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., U.K.) 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 Å silica gel. Thin-

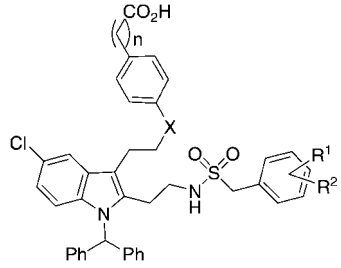
Table 2. Sulfonamide Analogues of **141**



compd	X	IC$_{50}$ (μM) GLU micelle[a]	IC$_{50}$ (μM) RWB TXB$_2$[b]	compd	X	IC$_{50}$ (μM) GLU micelle	IC$_{50}$ (μM) RWB TXB$_2$[b]
141	Ph	0.11	0.12	**91**	4-CN Ph	0.26	0.15
81	2-NO$_2$Ph	0.085	0.03	**93**	2-Pyr	0.4	0.35
83	3-NO$_2$Ph	0.11	0.07	**95**	3-Pyr	0.22	0.36
85	4-NO$_2$Ph	0.16	0.09	**97**	4-Pyr	0.18	0.34
87	2-CN Ph	0.06	0.07	**99**	cyclohexyl	0.20	0.15
89	3-CN Ph	0.30	0.16	**101**	2-napthyl	0.23	0.14

[a] Assay protocol reported previously.[41] Values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously.[41] Values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays.

Table 3. Effect of substitution on potency and clearance in the rat



compd	X	*n*	R^1	R^2	IC$_{50}$ (μM) GLU micelle[a]	IC$_{50}$ (μM) RWB TXB$_2$[b]	rat CL (mL/min)/kg[c]
141	O	0	H	H	0.11	0.12	69
24	CH$_2$	0	H	H	0.07	0.07	13
35	SO$_2$	0	H	H	0.02	0.08	54
45	SO$_2$	2	H	H	0.03	0.02	150
2	O	0	3-Cl	4-Cl	0.15	0.16	14
111	CH$_2$	0	3-Cl	4-Cl	0.04	0.07	5
113	SO$_2$	0	3-Cl	4-Cl	0.02	0.15	19
136	SO$_2$	2	3-Cl	4-Cl	0.04	0.04	10
103	O	0	2-Cl	H	0.05	0.05	>200
115	CH$_2$	0	2-Cl	H	0.02	0.03	7
117	SO$_2$	0	2-Cl	H	0.01	0.06	71
138	SO$_2$	2	2-Cl	H	0.01	0.02	63
105	O	0	2-Me	H	0.06	0.03	18
119	CH$_2$	0	2-Me	H	0.03	0.02	6
107	O	0	2-Me	6-Me	0.03	0.03	13
121	CH$_2$	0	2-Me	6-Me	0.01	0.03	3
123	SO$_2$	0	2-Me	6-Me	0.004	0.07	25
109	O	0	2-F	6-F	0.18	0.08	32
125	CH$_2$	0	2-F	6-F	0.06	0.36	10
127	SO$_2$	0	2-F	6-F	0.02	0.15	186
140	SO$_2$	2	2-F	6-F	0.07	0.02	52

[a] Assay protocol reported previously.[41] Values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously.[41] Values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays; [c] See Experimental Section for rat pharmacokinetic protocol.

Table 4. MC-9 Assay

compd	inhib LTB$_4$ (IC$_{50}$, μM)[a]	inhib PGF$_2\alpha$ (IC$_{50}$, μM)	inhib PGF$_2\alpha$ w/AA stimulation (IC$_{50}$, μM)
111	0.020	0.020	0.900
121	0.012	0.006	>1
zileuton	0.55	not active	not active
SC-560	not active	<0.005	<0.005
celecoxib	not active	0.40	0.30
naproxen	not active	0.20	0.33

[a] Assay protocol reported previously.[44] Values are generated from at least two runs, and each run consists of a mean value generated from duplicaate assays.

Table 5. Activity in Human Whole Blood Assays

mediator	% inhibition **121** at 0.039 μM[a]	% inhibition **111** at 0.15 μM
TXB$_2$	72[b]	57[d]
LTB$_4$	78[b]	64[d]
PGE$_2$	79[b]	78[d]
PGF$_{2\alpha}$	72[b]	66[d]
PAF	57[b]	50[c]

[a] Assay protocol reported previously.[44] [b] Average of 10 different donors. [c] Average of 2 different donors in 6 different experiments. [d] Average of 14 different donors.

Table 6. PO Efficacy in Short-Term Prostaglandin Dependent Models

compd	AUC (μM h)/ IC$_{50}$ (μM)[a]	ED$_{50}$ (mg/kg) for air pouch PGE$_2$ inhibition, po[b]	ED$_{50}$ (mg/kg) for CPE inhibition, po[c]
2	18	10–25	40
111	70	6	35
121	160	3.5	8

[a] The AUC was determined at 25 mg/kg po PK experiment, and the IC$_{50}$ is from the rat whole blood assay (see Experimental Section). [b] Data are derived from more than two independent dose response experiments for each compound, with six to eight mice per group (see Experimental Section for details). [c] Data are derived from more than three independent dose response experiments for each compound, with 10 mice per group (see Experimental Section for details).

layer chromatography (TLC) was performed using EMD 250 μm prescored silica gel 60 F$_{254}$ plates. Purity in two solvent systems (H$_2$O−CH$_3$CN and H$_2$O−MeOH) was determined using an Agilent 1100 HPLC instrument, and all final compounds were >95% pure (see Supporting Information for details).

General Procedure for Indole Reductive Alkylation. To the indole (1.0 equiv) and the aldehyde or acetal (1.1 equiv) in CH$_2$Cl$_2$ (0.06 M) at 0 °C was added HSiEt$_3$ (3.0 equiv) followed by TFA (3.0 equiv). After being stirred at 0 °C for 1 h, the reaction mixture was warmed to room temperature and the appearance of product detected by TLC. The reaction was then quenched with saturated sodium bicarbonate, diluted with CH$_2$Cl$_2$, washed with H$_2$O and brine, dried, and purified by column chromatography to yield the desired product.

General Procedure for Indole N-Alkylation with Bromodiphenylmethane. A solution of the indole (1.0 equiv) in DMF (0.6 M) was added to a mixture of sodium hydride (60% dispersion,

Table 7. Disease Severity Scores and Histological Scores in the Mouse CIA

compd[a]	mean disease severity score at day 31[b] ± SE (0–16)	histological severity score at day 31[c] (0–4)	plasma levels (ng/mL), peak concn[d]	plasma level (ng/mL), trough concn[e]
vehicle	6.7 ± 1.1	1.28		
2	4.6 ± 0.9	1.5	4085	531
111	0.83 ± 0.4	0.22	7195	2315
121	1.3 ± 0.7	0.23	923	118

[a] Compounds dosed 100 mg/kg PO, BID, with 10 mice /group, see experimental section for full details; [b] Each paw was scored daily using a 0–4 scale (4 is severe), the maximum score is 16. [c] see experimental section for full details, 4 is most severe [d] Samples by eye bleed at 1.5 h post dose for **2** and 3 h post dose for **111** and **121**. [e] Samples 12–14 h after last dose via end bleed.

Table 8. Histological Scoring of Synovitis and Cartilage Damage in the AIA Model

compd	total synovitis score[a] (0–11)	Mankin score,[64,b] (0–14)	plasma levels (ng/mL)[c] (4 h)	plasma level (ng/mL) (16 h)
vehicle	10.00 ± 1.38	8.83 ± 0.97		
111, 50 mg/kg	4.33 ± 2.14[d]	4.92 ± 1.24[e]	3598 ± 838	692 ± 493
111, 25 mg/kg	5.08 ± 2.71[d]	4.67 ± 2.27[e]	1126 ± 350	166 ± 45
111, 5 mg/kg	5.67 ± 1.69[d]	5.33 ± 1.21[e]	147 ± 106	34 ± 16
121, 50 mg/kg	4.75 ± 1.70[d]	5.25 ± 1.44[e]	1140 ± 487	110 ± 20
121, 25 mg/kg	6.58 ± 0.92[d]	6.25 ± 0.69[e]	698 ± 325	73 ± 31
121, 5 mg/kg	6.67 ± 1.75[d]	6.25 ± 0.76[e]	69 ± 44	26 ± 10
celecoxib, 5 mg/kg	4.42 ± 2.31[d]	5.17 ± 1.33[e]	1130 ± 336	129 ± 83

[a] Total score ± SD; 11 is most severe. [b] Total score ± SD; 14 is most severe. [c] Plasma at approximately t_{max}, ±SD (see Experimental Section for full details). [d] Plasma at trough levels, ±SD (see Experimental Section for full details). [e] Lower than vehicle, $P < 0.05$.

Table 9. PO Efficacy Data in Ascaris Suum Airway Challenge with Naturally Sensitized Sheep

compd[a]	early asthmatic response[b]	late asthmatic[c] response	AHR[d]
111	no effect	partial blockade	complete blockade
121	no effect	complete blockade	complete blockade

[a] Compounds dosed at 10 mg/kg b.i.d. 24 h before challenge and 2 h before challenge to generate the EAR and LAR data. Then a fourth dose was given 8 h after challenge, and 16 h later AHR was measured. $N = 2$ sheep. [b] No effect is defined as not significantly different from controls. [c] Partial blockade defined as approximately 50% reduction in lung resistance compared to controls 5–8 h after challenge. Complete blockade defined as approximately 85% reduction in lung resistance compared to controls 5–8 h after challenge. [d] Complete blockade defined as statistically equivalent amount of carbachol needed to achieve a 400% increase in resistance before and after antigen challenge.

1.1 equiv) in DMF (1.3 M) at 0 °C. The resulting brown reaction mixture was stirred for 0.5 h at 0 °C, and then bromodiphenylmethane (1.1 equiv, 2.5 M solution in DMF) was added. The mixture was allowed to warm to room temperature overnight and then subjected to aqueous workup. The organic layer was dried, filtered, and evaporated to a solid that was purified by silica gel chromatography.

General Procedure for Synthesis of Sulfonyl Chlorides A. Step 1. A mixture of halide (1.0 equiv) and sodium sulfite (1.2 equiv) in H_2O (0.1 M) and EtOH (0.2 M) was heated to reflux overnight. The mixture was cooled to room temperature and concentrated until a precipitate began to form. The product was collected by filtration and azeotroped with toluene. The resulting solid was used in the next step.

Step 2. To a suspension of the sodium sulfonate (1.0 equiv) in CH_2Cl_2 (0.1 M) were added DMF (0.7 equiv) and $SOCl_2$ (3.9 equiv). After 1.5 h, the white suspension was concentrated and azeotroped with toluene. The sulfonyl chlorides thus formed were used without further purification.

General Procedure for Synthesis of Sulfonyl Chlorides B. The benzyl halide (1.0 equiv), sodium sulfite (1.05 equiv), and TBAI (0.5 mg/mmol) were dissolved in H_2O (1.0 M) and warmed to 100 °C for 14 h. The mixture was cooled to room temperature, and the voluminous precipitate was collected by filtration and dried in a vacuum oven. The aqueous filtrate was saturated with NaCl at 100 °C and then cooled to 0 °C, and a second crop of crystalline sodium sulfate was collected by filtration and dried in vacuo. These two crops were combined and suspended in MeOH (0.09 M) to yield a hazy solution at room temperature. This was cooled to –10 to 0 °C, and HCl gas (3.75 equiv) was bubbled through the mixture at a rate that maintained the temperature below 0 °C. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 30 min, filtered, concentrated to an oil, and then azeotroped with toluene. This crude sulfonic acid was then dissolved in THF (0.5 M) and DMF (catalytic amount, 1 g of DMF/20 g of sulfonic acid) and cooled to –20 to –10 °C. Oxalyl chloride (3.5 equiv) was added slowly, and then the reaction was maintained at this temperature until LC/MS showed complete conversion to the desired sulfonyl chloride. The solvent volume was reduced in half in vacuo, the mixture was cooled to –20 to –10 °C, and then water was cautiously added to quench the excess oxalyl chloride. The THF/H_2O was further concentrated and then cooled to 10 °C to allow the desired sulfonyl chloride to precipitate. The sulfonyl chloride was collected by filtration, dried in vacuo at room temperature, and then used without further purification. Alternatively the sulfonyl chloride could be purified by low-temperature recrystallization from petroleum ether.

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 saturated $NaHCO_3$ (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.

General Procedure for Ester Hydrolysis. To a solution of the ester (1.0 mmol) in inhibitor free THF (0.5 M) was added 1 N aqueous NaOH or LiOH (3.0 mmol) and MeOH (0.5 M). 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 and acidified to pH 1 using 1 N HCl. The resulting mixture was extracted with EtOAc; the organic extracts were washed with H_2O and brine, then were dried, concentrated, and lyophilized to afford the carboxylic acid.

5-Chloro-1-(diphenylmethyl)-1*H*-indole-2-carbaldehyde (4). A solution of 5-chloroindole-2-carboxaldehyde **3**[73] (3.12 g, 17.3 mmol) in DMF was added to a suspension of NaH (0.83 g of 60% dispersion in mineral oil, 21 mmol) in DMF. After 30 min, a solution of bromodiphenylmethane (4.12 g, 14 mmol) in DMF was added. After 1 h aqueous workup was performed, and flash chromatography afforded the *N*-benzhydrylindole **4** (3.65 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, $J = 9.1$ Hz, 1 H), 6.95 (dd, $J = 9.2$, 2.1 Hz, 1 H), 7.04−7.47 (m, 11 H), 7.62 (d, $J = 1.6$ Hz, 1 H), 8.17 (s, 1 H), 9.82 (s, 1 H).

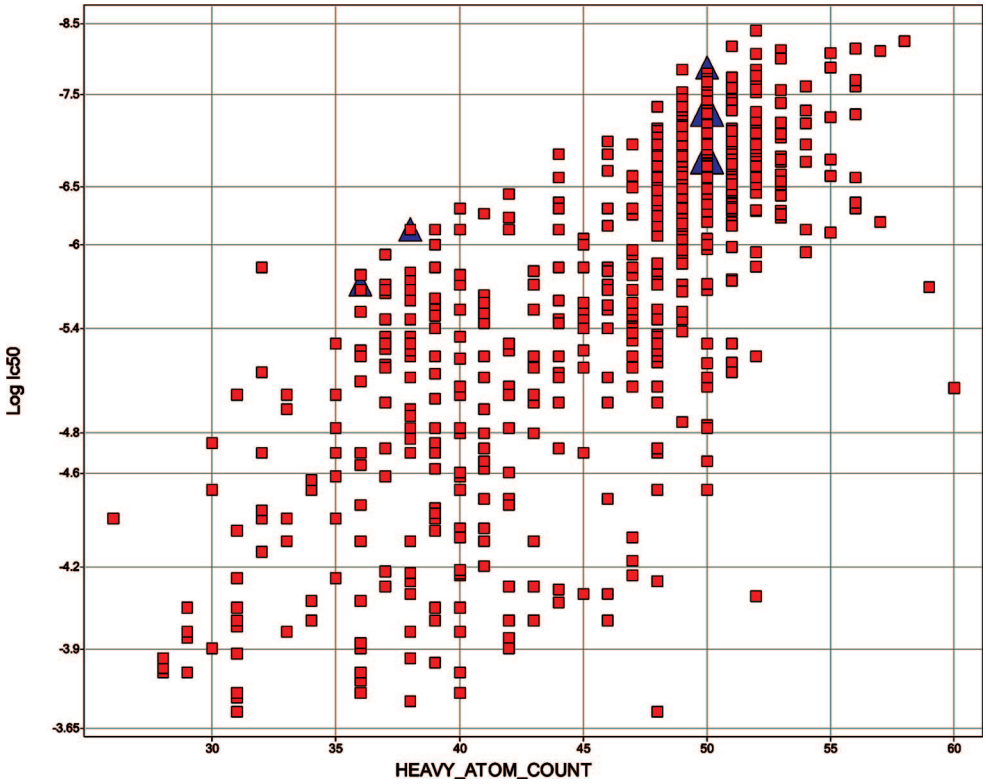


Figure 2. Atom efficiency of indole cPLA$_2\alpha$ inhibitors.

2-[5-Chloro-1-(diphenylmethyl)-1*H*-indol-2-yl]ethanamine (6). A mixture of aldehyde **4** (1.46 g, 4.2 mmol), NH_4OAc (1.30 g, 17 mmol), and $MeNO_2$ (40 mL) was heated to reflux for 2 h. The mixture was diluted with H_2O (100 mL) and brine (100 mL) and extracted with EtOAc (3 × 150 mL). Aqueous workup was performed to afford the nitro olefin, **5**, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 9.1 Hz, 1 H), 7.01−7.21 (m, 7 H), 7.31−7.41 (m, 6 H), 7.46 (d, J = 13.2 Hz, 1 H), 7.62 (d, J = 1.6 Hz, 1 H), 7.88 (d, J = 13.2 Hz, 1 H). To a solution of the crude nitro olefin (1.64 g, 4.2 mmol) in THF (100 mL) and concentrated HCl (10 mL) was added Zn(Hg) (prepared by shaking Zn dust (5.5 g, 84 mmol) and $HgCl_2$ (0.55 g, 1.2 mmol) in 5% aqueous HCl (10 mL) and decanting the aqueous phase). The nitro olefin mixture was heated to reflux for 1.5 h, cooled to room temperature, and filtered through Celite. Concentrated aqueous NH_4OH solution (200 mL) was added to the filtrate, and the resulting mixture was stirred for 15 min. THF was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (gradient elution with 1% MeOH−0.1% Et_3N−CH_2Cl_2 to 10% MeOH−CH_2Cl_2) afforded the amine **6** (0.53 g, 35% yield, two steps) as a pale-yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (br s, 2 H), 2.85 (t, J = 6.7 Hz, 2 H), 2.97 (t, J = 6.5 Hz, 2 H), 6.35 (s, 1 H), 6.53 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 6.90 (s, 1 H), 7.02−7.17 (m, 4 H), 7.27−7.37 (m, 6 H), 7.49 (d, J = 1.9 Hz, 1 H).

***N*-{2-[5-Chloro-1-(diphenylmethyl)-1*H*-indol-2-yl]ethyl}-1-phenylmethanesulfonamide (7).** Amine **6** (1.1 g, 3.0 mmol), α-toluenesulfonyl chloride (0.64 g, 3.3 mmol), and saturated aqueous $NaHCO_3$ (25 mL) were reacted according to the general Schotten−Baumann procedure. After 3 h aqueous workup was performed to afford the sulfonamide **7** (1.4 g, 90% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (t, J = 6.9 Hz, 2 H), 3.07 (q, J = 6.7 Hz, 2 H), 4.11 (s, 2 H), 4.17 (t, J = 6.0 Hz, 1 H), 6.24 (s, 1 H), 6.55 (d, J = 9.1 Hz, 1 H), 6.76−6.95 (m, 2 H), 7.07 (dd, J = 5.6, 3.7 Hz, 4 H), 7.14−7.22 (m, 2 H), 7.22−7.38 (m, 9 H), 7.47 (d, J = 1.6 Hz, 1 H).

Methyl 4-{[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]methyl}benzoate (8). The general reductive alkylation procedure was followed utilizing indole **7** (225 mg, 0.43 mmol), methyl 4-formylbenzoate (79 mg, 0.48 mmol), Et_3SiH (0.21 mL, 1.3 mmol), and TFA (67 μL, 0.87 mmol). After 8 h, aqueous workup was performed, followed by flash chromatography (gradient elution with 10−30% EtOAc−hexanes) to afford the C3 alkylated indole **8** (107 mg, 37% yield) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40−2.53 (m, 2 H), 2.72−2.82 (m, 2 H), 3.72 (s, 3 H), 3.79−3.84 (m, 2 H), 3.90−3.95 (m, 2 H), 6.35 (d, J = 8.8 Hz, 1 H), 6.64 (dd, J = 8.8, 1.9 Hz, 1 H), 6.73 (s, 1 H), 6.88−6.98 (m, 7 H), 6.99−7.08 (m, 3 H), 7.08−7.12 (m, 2 H), 7.13−7.20 (m, 5 H), 7.75 (d, J = 8.2 Hz, 2 H).

4-{[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]methyl}benzoic acid (9). Hydrolysis of the methyl ester (107 mg, 0.16 mmol) according to the general procedure afforded the carboxylic acid **9** (80 mg, 75% yield) as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.65−2.86 (m, 4 H), 3.87−3.93 (m, 2 H), 3.99−4.06 (m, 2 H), 6.24 (d, J = 8.8 Hz, 1 H), 6.58 (d, J = 10.7 Hz, 1 H), 6.86−6.92 (m, 5 H), 6.97−7.03 (m, 2 H), 7.04−7.13 (m, 6 H), 7.14−7.24 (m, 6 H), 7.59−7.67 (m, 2 H).

Methyl (4-{[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]methyl}phenoxy)acetate (10). Using the general reductive alkylation procedure, indole **7** (200 mg, 0.39 mmol) was reacted with methyl (4-formylphenoxy)acetate[74] (83 mg, 0.42 mmol) to afford the C3 alkylated indole **10** (50 mg, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35−2.46 (m, 2 H), 2.71−2.81 (m, 2 H), 3.59−3.61 (m, 3 H), 3.79−3.83 (m, 4 H), 4.42−4.46 (m, 2 H), 6.32 (d, J = 8.8 Hz, 1 H), 6.58−6.66 (m, 2 H), 6.69 (s, 1 H), 6.86−6.93 (m, 5 H), 6.93−7.00 (m, 3 H), 7.05−7.11 (m, 4 H), 7.11−7.18 (m, 6 H), 7.21 (d, J = 2.2 Hz, 1 H).

(4-{[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]methyl}phenoxy)acetic acid (11). Hydrolysis of the methyl ester (46 mg, 0.066 mmol) according to the general procedure afforded the carboxylic acid **11** (27 mg, 61% yield) as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78−2.98

(m, 6 H), 3.94 (s, 2 H), 4.20−4.24 (m, 2 H), 6.41 (d, J = 8.8 Hz, 1 H), 6.67−6.78 (m, 3 H), 6.98−7.09 (m, 7 H), 7.21−7.31 (m, 5 H), 7.31−7.44 (m, 7 H).

Methyl 3-(4-{[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]methyl}phenyl)propanoate (12). Using the general reductive alkylation procedure, indole **7** (220 mg, 0.42 mmol) was reacted with the methyl 3-(4-formylphenyl)-propanoate[75] (76 mg, 0.39 mmol) to afford the C3 alkylated indole **12** (50 mg, 7% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37−2.52 (m, 4 H), 2.65−2.82 (m, 4 H), 3.47 (s, 3 H), 3.79 (s, 2 H), 3.85 (s, 2 H), 6.33 (d, J = 8.8 Hz, 1 H), 6.63 (dd, J = 8.8, 2.2 Hz, 1 H), 6.71 (s, 1 H), 6.88−6.98 (m, 9 H), 7.03−7.11 (m, 5 H), 7.13−7.18 (m, 5 H), 7.20 (d, J = 1.9 Hz, 1 H).

3-(4-{[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]methyl}phenyl)propanoic acid (13). Hydrolysis of the methyl ester (50 mg, 0.072 mmol) according to the general procedure afforded the carboxylic acid **13** (32 mg, 65% yield) as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15−2.26 (m, 2 H), 2.50−2.61 (m, 2 H), 2.64−2.84 (m, 4 H), 3.79 (s, 2 H), 4.03 (s, 2 H), 6.24 (d, J = 9.1 Hz, 1 H), 6.57 (dd, J = 8.8, 1.9 Hz, 1 H), 6.85−6.92 (m, 8 H), 7.03−7.12 (m, 6 H), 7.14−7.24 (m, 7 H).

4,4-Diethoxy-*N*′-hydroxybutanimidamide. A mixture of 4,4-diethoxybutanenitrile (3.0 g, 19.1 mmol) and hydroxylamine (50 wt % in water, 4.2 g, 63.6 mmol) was stirred for 3 days. The volatiles were removed under high vacuum to give the hydroxyamidine in quantitative yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, J = 7.0 Hz, 6 H), 1.65−1.79 (m, 2 H), 1.93–2.06 (m, 2 H), 3.37−3.51 (m, 2 H), 3.51−3.64 (m, 2 H), 4.46 (t, J = 5.6 Hz, 1 H), 5.35 (s, 2 H), 8.74 (s, 1 H).

Ethyl [3-(3,3-Diethoxypropyl)-1,2,4-oxadiazol-5-yl]acetate. To the hydroxyamidine (1.79 g, 9.4 mmol) in THF (30 mL) under nitrogen was added NaH (400 mg, 60% in mineral oil, 10 mmol). The mixture was heated to 50 °C for 1 h. The mixture was cooled to room temperature, and diethyl malonate (4.3 mL, 28.3 mmol) was added dropwise. The resulting mixture was heated to 85 °C for 1 h. The mixture was concentrated and purified by flash chromatography (10% EtOAc−hexane) to afford the oxadiazole (1.4 g) in 52% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (t, J = 7.0 Hz, 6 H), 1.00 (t, J = 7.1 Hz, 3 H), 1.65−1.74 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 3.17−3.29 (m, 2 H), 3.32−3.44 (m, 2 H), 3.95 (q, J = 7.1 Hz, 2 H), 4.04 (s, 2 H), 4.32 (t, J = 5.5 Hz, 1 H).

(3-{3-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}-1,2,4-oxadiazol-5-yl)acetic acid (15). To a mixture of **7** (90 mg, 0.17 mmol), oxadiazole (54 mg, 0.19 mmol), and Et_3SiH (84 μL, 0.53 mmol) under nitrogen was added TFA dropwise (41 μL, 0.53 mmol) according to the general reductive alkylation procedure. The mixture was concentrated and purified by preparative TLC to afford indole **14** in 54% yield (65 mg). The ethyl ester intermediate was hydrolyzed according to the general procedure to afford the title acid **15** (60 mg, 96% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.64−1.77 (m, 2 H), 2.37−2.71 (m, 8 H), 3.41 (s, 2 H), 4.09 (s, 2 H), 6.23 (d, J = 8.8 Hz, 1 H), 6.58 (dd, J = 8.8, 2.2 Hz, 1 H), 6.72−7.05 (m, 7 H), 7.05−7.25 (m, 9 H), 7.38 (d, J = 1.9 Hz, 1 H), 7.82 (s, 1 H).

Methyl 3-(4-{2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}phenyl)propanoate (16). Using the general reductive alkylation procedure, **7** (220 mg, 0.43 mmol) was reacted with methyl 3-[4-(2-oxoethoxy)phenyl]propanoate[76] (150 mg, 0.65 mmol) to afford the C3 alkylated indole **16** (90 mg, 30% yield).

3-{4-[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)amino]ethyl}-5-chloro-1*H*-indol-3-yl)ethoxy]phenyl}propanoic acid (17). Hydrolysis of the methyl ester (90 mg, 0.13 mmol) according to the general procedure afforded the carboxylic acid **17** (66 mg, 75% yield), mp 94.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (t, J = 7.3 Hz, 2H), 2.70−2.84 (m, 4H), 2.86 (t, 2H), 3.08 (t, J = 6.3 Hz, 2H), 4.04 (s, 2H), 4.22 (t, J = 6.3 Hz, 1H), 4.70 (s, 1H), 6.38−6.54 (d, J = 9.1 Hz, 1 H), 6.75 (d, J = 8.6 Hz, 2H), 6.79 (dd, J = 8.9, 2.1 Hz, 1H), 6.83 (s, 1H), 7.02−7.11 (m, 6H), 7.13−7.25 (m, 5H), 7.28−7.35 (m, 6H), 7.49 (d, J = 2.1 Hz, 1H). HRMS calcd for [$C_{41}H_{39}ClN_2O_5S$ + H] 705.219 54; found 705.219 28. Anal. ($C_{41}H_{39}ClN_2O_5S$) C, H, N.

Methyl 4-[3-(5-Chloro-2-methyl-1*H*-indol-3-yl)propyl]benzoate (18). 5-Chloro-2-methylindole (0.86 g, 5.2 mmol), methyl 4-(2-formylethyl)benzoate[77] (1.0 g, 5.2 mmol), TFA (1.78 g, 15.6 mmol), and Et_3SiH (1.81 g, 15.6 mmol) were reacted according to the general reductive alkylation procedure. The residue was purified by flash column chromatography with 10–20% EtOAc−hexanes to yield the desired **18** (1.67 g, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88−2.04 (m, 2 H), 2.33 (s, 3 H), 2.65−2.76 (m, 4 H), 3.87−3.94 (m, 3 H), 7.06 (m, 1 H), 7.18 (m, 2 H), 7.24 (s, 1 H), 7.41 (d, J = 1.9 Hz, 1 H), 7.76 (s, 1 H), 7.96 (d, J = 8.2 Hz, 2 H).

Methyl 4-{3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]propyl}benzoate (19). 18(1.66 g, 4.86 mmol) was treated with NaH (60% in mineral oil, 0.24 g, 5.83 mmol) and bromodiphenylmethane (1.8g, 7.29 mmol) in DMF (5 mL) as described in the general N-alkylation procedure, and flash chromatography (10% EtOAc−hexanes) delivered **19** (1.47 g, 59% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−1.99 (m, 2 H), 2.15 (s, 3 H), 2.61−2.74 (m, 4 H), 3.84−3.89 (s 3 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.7, 2.1 Hz, 1 H), 6.82 (s, 1 H), 7.03−7.09 (m, 4 H), 7.19 (d, J = 8.2 Hz, 2 H), 7.22−7.24 (m, 1 H), 7.26−7.32 (m, 5 H), 7.38 (d, J = 1.9 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 2 H).

Methyl 4-{3-[5-Chloro-1-(diphenylmethyl)-2-formyl-1*H*-indol-3-yl]propyl}benzoate (20). To a solution of **19** (1.46 g, 2.87mmol) in CCl_4 (14.5 mL) was added NBS (1.02 g, 5.73 mmol) and benzoyl peroxide (2 mg). The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and filtered, and the solid was washed with CCl_4. The filtrate was evaporated to afford a brown residue that was dissolved in acetone (40 mL) and water (4 mL). Ag_2CO_3 (1.75 g, 3.16 mmol) was then added, and the resulting suspension was stirred overnight. The mixture was filtered through Celite, the solvent was evaporated under reduced pressure, and the residue was taken up in H_2O, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10% EtOAc−hexanes) afforded **20** (1.13 g) in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98−2.14 (m, 2 H), 2.76 (t, J = 7.7 Hz, 2 H), 3.07 (m, 2 H), 3.89 (s, 3 H), 6.61 (d, J = 9.1 Hz, 1 H), 6.99 (dd, J = 9.1, 2.2 Hz, 1 H), 7.09−7.14 (m, 4 H), 7.21 (s, 1 H), 7.26−7.31 (m, 7 H), 7.55 (d, J = 2.2 Hz, 1 H), 7.95 (d, J = 8.2 Hz, 2 H), 8.21 (s, 1 H), 10.02 (s, 1 H).

Methyl 4-(3-{5-Chloro-1-(diphenylmethyl)-2-[(*E*)-2-nitrovinyl]-1*H*-indol-3-yl}propyl)benzoate (21). To a solution of **20** (0.52 g, 1.0 mmol) in CH_3NO_2 (6.2 mL) was added NH_4OAc (0.077 g, 1.0 mmol), and the mixture was heated to reflux for 1 h. Additional NH_4OAc (0.077 g, 1.0 mmol) was then added, and heating at reflux was continued for an additional 1 h. NH_4OAc (0.077 g, 1.0 mmol) was added again, and the heating continued for a further 1 h. The reaction mixture was cooled to room temperature, and aqueous workup was performed followed by flash chromatography (10% EtOAc−hexanes) to yield the nitro olefin **21** (0.38 g, 68% yield) as a yellow foam.

Methyl 4-{3-[2-(2-Aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (22). Zn(Hg) was made by adding $HgCl_2$ (3.4 g, 7.2 mmol) to a mixture of Zn dust (34.7 g, 530 mmol) and 5% HCl (38 mL) and stirring this vigorously for 10 min. The aqueous phase was decanted and washed with 38 mL of 5% HCl. This solid was added to a mixture of the nitro olefin **21**(15 g, 26.6 mmol) in THF (660 mL) and concentrated HCl (65 mL). This mixture was stirred at room temperature for 1 h, then at reflux for 15 min. The reaction mixture was cooled to room temperature and filtered through Celite. Concentrated aqueous NH_4OH solution (200 mL) was added to the filtrate, the resulting mixture was stirred for 15 min, and THF was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated to afford a brown foam that was purified by column chromatography (0−2% MeOH−$CHCl_3$) to isolate the desired amine **22** (6.1 g, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (t, J = 7.7 Hz, 2 H), 2.69−2.80 (m, 6 H), 2.84 (t, J = 7.2 Hz, 2 H), 3.85−3.93 (s, 3 H),

6.48 (d, J = 8.8 Hz, 1 H), 6.77 (dd, J = 8.8, 2.0 Hz, 1 H), 6.89 (s, 1 H), 7.05−7.12 (m, 4 H), 7.23 (s, 1 H), 7.27−7.33 (m, 7 H), 7.41 (d, J = 2.0 Hz, 2 H), 7.95 (d, J = 8.3 Hz, 2 H).

Methyl 4-{3-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (23). The amine (1.5 g, 2.79 mmol) was reacted with α-toluenesulfonyl chloride according to the general Schotten−Baumann procedure to afford sulfonamide **23** (1.62 g, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90−2.01 (m, 2 H), 2.67−2.80 (m, 6 H), 2.88−2.96 (m, 2 H), 3.91 (s, 3 H), 4.00 (t, J = 6.0 Hz, 1 H), 4.03−4.05 (m, 2 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.2 Hz, 1 H), 6.84−6.86 (m, 1 H), 7.04−7.09 (m, 5 H), 7.15 (d, J = 1.6 Hz, 1 H), 7.17−7.19 (m, 1 H), 7.24−7.26 (m, 2 H), 7.26−7.28 (m, 2 H), 7.30−7.35 (m, 6 H), 7.41 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 8.2 Hz, 2 H).

4-{3-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (24). Ester **23** (1.59 g, 2.3 mmol) was hydrolyzed using the general procedure to afford the desired product (1.56 g) in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90−2.02 (m, 2 H), 2.69−2.81 (m, 4 H), 3.73−3.79 (m, 4 H), 4.05 (s, 2 H), 4.10−4.18 (m, 1 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.2 Hz, 1 H), 6.84−6.86 (m, 1 H), 7.03−7.10 (m, 5 H), 7.14−7.16 (m, 1 H), 7.16−7.19 (m, 2 H), 7.25 (s, 1 H), 7.30 (s, 2 H), 7.31−7.36 (m, 6 H), 7.41 (d, J = 1.9 Hz, 1 H), 8.01 (d, J = 8.2 Hz, 2 H). HRMS calcd for $[C_{40}H_{37}ClN_2O_4S + H]$ 677.2235 found 677.224.

2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1*H*-indole (26). 2-(5-Chloro-1*H*-indol-2-yl)ethanol **25**[50] (13.7 g, 70.0 mmol) was added to a solution (under N_2) containing tBDMSCl (22 mL, 84.6 mmol), imidazole (11.9 g, 175.2 mmol), and DMF (1.8 M). The reaction mixture was stirred overnight, quenched with saturated aqueous $NaHCO_3$, and subjected to an aqueous workup which delivered, after purification via flash chromatography (30% hexanes/CH_2Cl_2), **26** (28.2 g, 95% yield) as a yellow oil.

Methyl 4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1*H*-indol-3-yl]ethyl}thio)benzoate (27). Indole **26** (10.1 g, 23.3 mmol), methyl 4-[(2-oxoethyl)sulfanyl]benzoate[41] (18.2 g, 86.6 mmol), TFA (5.4 mL, 70.1 mmol), Et_3SiH (44 mL, 275.5 mmol) were treated following the general reductive alkylation procedure to yield, after purification via flash chromatography (20% EtOAc/hexane), **27** (11.5 g, 79% yield) as a yellow solid.

Methyl 4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}thio)benzoate (28). Indole **27** (11.6 g, 18.4 mmol), NaH (0.81 g, 20.3 mmol), and bromodiphenylmethane (8.2 g, 33.2 mmol) were reacted using the general N-alkylation conditions to afford, after purification via flash chromatography (20% EtOAc/hexanes), **28** (9.5 g, 65% yield) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9 H), 2.94−3.07 (m, 4 H), 3.16 (t, J = 7.6 Hz, 2 H), 3.65 (t, J = 7.3 Hz, 2 H), 3.90 (s, 3 H), 6.39 (d, J = 8.8 Hz, 1 H), 6.69 (s, 1 H), 6.75 (dd, J = 8.8, 2.0 Hz, 1 H), 6.92 (d, J = 7.1 Hz, 3 H), 7.15−7.30 (m, 11 H), 7.30−7.43 (m, 5 H), 7.44−7.54 (m, 3 H), 7.71 (dd, J = 7.7, 1.9 Hz, 1 H), 7.85−7.94 (m, 2 H).

Methyl 4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (29). NMO (6.45 g, 55.1 mmol) was added to a solution containing silyl ether **28** (7.27 g, 9.15 mmol), CH_3CN (0.1 M), and molecular sieves (1 g/mmol of benzoate). After 10 min, TPAP (0.39 g, 1.11 mmol) was added and the mixture was heated to 40 °C. After 1.5 h the reaction mixture was cooled and filtered. The filtrate was purified via flash chromatography (20% EtOAc/hexanes) to deliver **29** (5.30 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9 H), 2.99 (t, J = 6.9 Hz, 2 H), 3.11−3.18 (m, 2 H), 3.24−3.31 (m, 2 H), 3.64 (t, J = 6.8 Hz, 2 H), 3.97 (s, 3 H), 6.35 (d, J = 8.8 Hz, 1 H), 6.65 (s, 1 H), 6.73 (dd, J = 8.8, 2.0 Hz, 1 H), 6.87 (d, J = 7.3 Hz, 4 H), 7.10 (d, J = 2.0 Hz, 1 H), 7.16−7.28 (m, 9 H), 7.33−7.39 (m, 2 H), 7.42−7.51 (m, 4 H), 7.96 (d, J = 8.6 Hz, 3 H), 8.19 (d, J = 8.6 Hz, 2 H).

Methyl 4-({2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (30). TBAF (7.9 mL, 7.9 mmol, 1.0 M solution in THF) was added to a solution of silyl ether **29** (5.42 g, 6.56 mmol) and THF (0.1 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and after 1 h was quenched with aqueous NH_4Cl solution. Aqueous workup and purification via flash chromatography (10% EtOAc/CH_2Cl_2) delivered **30** (3.31 g, 86% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (t, J = 6.3 Hz, 2 H), 3.16−3.25 (m, 2 H), 3.40−3.47 (m, 2 H), 3.65 (q, J = 6.0 Hz, 2 H), 3.98 (s, 3 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.9, 2.1 Hz, 1 H), 6.92 (s, 1 H), 7.02−7.08 (m, 4 H), 7.17 (d, J = 1.8 Hz, 1 H), 7.26−7.34 (m, 6 H), 7.98−8.09 (m, 2 H), 8.18−8.27 (m, 2 H).

Methyl 4-{[2-(5-Chloro-1-(diphenylmethyl)-2-{2-[(methylsulfonyl)oxy]ethyl}-1*H*-indol-3-yl)ethyl]sulfonyl}benzoate (31). MsCl (0.69 mL, 8.91 mmol) and Et_3N (1.55 mL, 11.1 mmol) were added to a solution of alcohol **30** (2.62 g, 4.45 mmol) in CH_2Cl_2 (0.02 M) at 0 °C. After 1 h, the reaction mixture was warmed to room temperature. After 1 h, aqueous workup was performed and concentration afforded **31** (2.93 g, 86% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 3 H), 3.22 (t, J = 6.3 Hz, 4 H), 3.38−3.46 (m, 2 H), 3.95−3.99 (m, 3 H), 4.01 (t, J = 6.8 Hz, 2 H), 6.48−6.54 (m, 1 H), 6.79−6.85 (m, 1 H), 6.87 (s, 1 H), 7.02−7.09 (m, 4 H), 7.27−7.36 (m, 7 H), 8.01−8.10 (m, 2 H), 8.23 (dd, J = 8.6, 1.8 Hz, 2 H).

Methyl 4-({2-[2-(2-Azidoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (32). A mixture of indole **31** (2.89 g, 4.34 mmol), sodium azide (1.43 g, 22.0 mmol), and DMF (0.05 M) was heated to 60 °C. After 1 h the reaction mixture was cooled and an aqueous workup was performed to afford **32** (2.67 g, 99% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 3.01 (t, J = 7.2 Hz, 2 H), 3.04−3.11 (m, 2 H), 3.21 (t, J = 7.1 Hz, 2 H), 3.48−3.55 (m, 2 H), 3.82 (s, 3 H), 6.48 (d, J = 8.6 Hz, 1 H), 6.66 (dd, J = 9.0, 2.1 Hz, 1 H), 6.96−7.03 (m, 4 H), 7.07 (s, 1 H), 7.16 (d, J = 1.8 Hz, 1 H), 7.20−7.27 (m, 6 H), 8.01 (d, J = 8.6 Hz, 2 H), 8.08−8.14 (m, 2 H).

Methyl 4-({2-[2-(2-Aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (33). Azide **32** (2.64 g, 4.31 mmol), PPh_3 (2.30 g, 8.70 mmol), and THF (0.1 M) were placed together under N_2 and stirred overnight. H_2O (1 mL/mmol benzoate) was added, and reaction mixture was stirred overnight. The solution was concentrated and purified via flash chromatography (gradient elution 75% EtOAc/hexanes followed by 5% MeOH/CH_2Cl_2) to afford **33** (2.52 g, 99% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (d, J = 6.5 Hz, 2 H), 2.83−2.92 (m, 2 H), 3.14−3.26 (m, 2 H), 3.38−3.49 (m, 2 H), 3.98 (s, 3 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.8, 2.3 Hz, 1 H), 6.88 (s, 1 H), 7.14 (d, J = 2.0 Hz, 1 H), 7.22−7.34 (m, 5 H), 7.46 (d, J = 3.0 Hz, 1 H), 7.50 (m, 5 H), 7.62−7.72 (m, 1 H), 8.05 (d, J = 8.6 Hz, 2 H), 8.24 (d, J = 8.3 Hz, 2 H).

Methyl 4-({2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (34). α-Toluenesulfonyl chloride (0.094 g, 0.49 mmol) and amine **33** (0.14 g, 0.25 mmol), were reacted following the general Schotten−Baumann procedure. After 2 h, aqueous workup and purification by silica gel preparatory plate (3% MeOH in CH_2Cl_2) delivered **34** (0.17 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, J = 6.6 Hz, 2 H), 2.95 (t, J = 7.1 Hz, 2 H), 3.13−3.21 (m, 2 H), 3.34−3.41 (m, 2 H), 3.97 (s, 3 H), 4.08 (s, 2 H), 4.34 (t, J = 6.3 Hz, 1 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.78 (dd, J = 8.9, 2.14 Hz, 1 H), 6.81 (s, 1 H), 7.01−7.07 (m, 4 H), 7.18−7.23 (m, 3 H), 7.27−7.33 (m, 9 H), 8.03 (d, J = 8.6 Hz, 2 H), 8.22 (d, J = 8.6 Hz, 2 H).

4-{[2-(1-Benzhydryl-2-{2-[(benzylsulfonyl)amino]ethyl}-5-chloro-1*H*-indol-3-yl)ethyl]sulfonyl}benzoic Acid (35). Ester **34** (0.13 g, 0.18 mmol) was hydrolyzed using the general procedure to afford the desired product **35** (0.12 g, 92% yield), mp 97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, J = 6.6 Hz, 2H), 2.95 (d, J = 6.8 Hz, 2H), 3.13−3.24 (m, 2H), 3.34−3.44 (m, 2H), 4.09 (s, 2H), 4.43 (t, J = 6.1 Hz, 1H), 6.47 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 9.1, 2.1 Hz, 1H), 6.81 (s, 1H), 7.05 (dd, J = 6.6, 2.8 Hz, 4H), 7.19−7.23 (m, 3H), 7.27−7.34 (m, 9H), 8.06 (d, J = 8.6 Hz, 2H), 8.24 (d, J = 8.3 Hz, 2H). HRMS calcd $[C_{39}H_{35}ClN_2O_6S_2 + H]$ 725.155 23; found 725.154 37.

3-(2-Bromoethyl)-2-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indole (37). To a solution of alcohol **36** (1.085 g, 1.7 mmol) in CH_2Cl_2 (0.08 M) was added 1,3-bis(diphenylphosphino)propane (0.52 g, 1.3 mmol). The solution was cooled to 0 °C under N_2, and CBr_4 (0.69 g, 2.1 mmol) was added. The mixture was warmed to room temperature over 2 h, concentrated, and purified via flash chromatography (40% CH_2Cl_2/hexanes) to give **37** (0.33 g, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (m, 9 H), 3.02−3.12 (m, 3 H), 3.18 (t, J = 7.9 Hz, 1 H), 3.46 (t, J = 7.9 Hz, 1 H), 3.60 (t, J = 7.8 Hz, 1 H), 3.66 (t, J = 7.1 Hz, 2 H), 6.39 (d, J = 8.8 Hz, 1 H), 6.71 (s, 1 H), 6.73−6.78 (m, 1 H), 6.92 (d, J = 7.1 Hz, 4 H), 7.15−7.30 (m, 8 H), 7.30−7.40 (m, 4 H), 7.43 (d, J = 2.0 Hz, 1 H), 7.48−7.55 (m, 4 H).

Methyl 3-[4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}thio)phenyl]propanoate (38). To a solution of bromide **37** (3.6 g, 5.1 mmol) in DMF (0.1 M) were added methyl 3-(4-mercaptophenyl)propanoate[41] (1.51 g, 7.7 mmol) and K_2CO_3 (1.1 g, 7.7 mmol). After 2 h, aqueous workup followed by purification by flash chromatography (CH_2Cl_2) afforded **38** (3.37 g, 80% yield).

Methyl 3-[4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]-propanoate (39). NMO (2.0 g, 16.4 mmol) was added to a solution containing silyl ether **38** (3.35 g, 4.1 mmol), CH_3CN (0.1 M), and molecular sieves (1 g/mmol benzoate). After 10 min, TPAP (0.75 g, 0.20 mmol) was added and the mixture was heated to 40 °C. After 1.5 h the reaction mixture was cooled, and the filtrate was collected and purified via flash chromatography (gradient elution 0−1% EtOAc−CH_2Cl_2) to deliver **39** (1.53 g, 44% yield) as a white foam.

Methyl 3-[4-({2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (40). TBAF (2.1 mL, 2.1 mmol, 1.0 M solution in THF) was added to a solution of silyl ether **39** (1.5 g, 1.8 mmol) and THF (0.1 M) at 0 °C. The reaction mixture was allowed to warm to room temperature, and after 1 h it was quenched with aqueous NH_4Cl solution. Aqueous workup and purification via flash chromatography (gradient elution 10−25% EtOAc−CH_2Cl_2) delivered **40** (1.0 g, 90% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64−2.72 (m, 2 H), 2.97 (t, J = 6.5 Hz, 2 H), 3.02−3.09 (m, 2 H), 3.12−3.20 (m, 2 H), 3.34−3.41 (m, 2 H), 3.60−3.65 (m, 2 H), 3.67 (s, 3 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.71−6.79 (m, 2 H), 6.92 (s, 1 H), 7.03−7.08 (m, 3 H), 7.10−7.17 (m, 2 H), 7.27−7.33 (m, 5 H), 7.41−7.45 (m, 2 H), 7.89 (d, J = 8.3 Hz, 2 H).

Methyl 3-(4-{[2-(5-Chloro-1-(diphenylmethyl)-2-{2-[(methylsulfonyl)oxy]ethyl}-1*H*-indol-3-yl)ethyl]sulfonyl}phenyl)propanoate (41). MsCl (0.15 mL, 2.0 mmol) and Et_3N (0.35 mL, 2.5 mmol) were added to a solution of alcohol **40** (0.615 g, 1.0 mmol) in CH_2Cl_2 (0.02 M) at 0 °C under N_2. After 1 h the reaction mixture was warmed to room temperature and stirred for 1 h. Aqueous workup afforded **41** (0.730 g) in quantitative yield.

Methyl 3-[4-({2-[2-(2-Azidoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (42). To mesylate **41** (0.228 g, 0.33 mmol) in DMF (0.03 M) was added NaN_3 (0.065 g, 1.0 mmol). The mixture was heated to 60 °C for 2 h and cooled and an aqueous workup was performed to afford **42** (0.250 g) in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63−2.71 (m, 2 H), 2.92−2.97 (m, 2 H), 3.03−3.10 (m, 2 H), 3.12−3.21 (m, 4 H), 3.34−3.41 (m, 2 H), 3.67 (s, 3 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.0 Hz, 1 H), 6.87 (s, 1 H), 7.02−7.09 (m, 4 H), 7.10−7.15 (m, 2 H), 7.29−7.34 (m, 5 H), 7.41−7.46 (m, 2 H), 7.88−7.92 (m, 2 H).

Methyl 3-[4-({2-[2-(2-Aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (43). Azide **42** (0.25 g, 0.39 mmol), PPh_3 (0.113 g, 0.43 mmol), and THF (0.1 M) were stirred overnight. Water (1 mL/mmol benzoate) was added, and reaction mixture was again stirred overnight. The solution was concentrated and purified via flash chromatography (4% MeOH−CH_2Cl_2) to afford **43** (0.17 g, 71% yield) as a white foam.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64−2.71 (m, 2 H), 2.73 (t, J = 6.9 Hz, 2 H), 2.87 (t, J = 7.1 Hz, 2 H), 3.03−3.09 (m, 2 H), 3.13−3.20 (m, 2 H), 3.33−3.40 (m, 2 H), 3.67 (s, 3 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.75 (dd, J = 8.9, 2.1 Hz, 1 H), 6.88 (s, 1 H), 7.01−7.07 (m, 4 H), 7.09 (d, J = 2.0 Hz, 1 H), 7.27−7.32 (m, 6 H), 7.43 (d, J = 8.6 Hz, 2 H), 7.90 (d, J = 8.3 Hz, 2 H).

Methyl 3-[4-({2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (44). Amine **43** (0.100 g, 0.16 mmol), α-toluenesulfonyl chloride (0.035 g, 0.18 mmol), and saturated aqueous $NaHCO_3$ were reacted according to the general Schotten−Baumann procedure. Aqueous workup and purification by chromatography (2% MeOH/CH_2Cl_2) delivered sulfonamide **44** (0.116 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (t, J = 7.6 Hz, 2 H), 2.80−2.96 (m, 4 H), 3.04 (t, J = 7.6 Hz, 2 H), 3.08−3.14 (m, 2 H), 3.28−3.35 (m, 2 H), 3.66 (s, 3 H), 4.08 (s, 2 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.72 (dd, J = 7.4, 1.9 Hz, 1 H), 6.77 (dd, J = 8.9, 2.1 Hz, 1 H), 6.80−6.84 (m, 1 H), 7.01−7.07 (m, 4 H), 7.16−7.20 (m, 2 H), 7.20−7.24 (m, 2 H), 7.28−7.34 (m, 7 H), 7.40 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 8.3 Hz, 2 H).

3-[4-({2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoic acid (45). Ester **44** (0.087 g, 0.11 mmol) was hydrolyzed using the general procedure to afford **45** (0.079 g, 92% yield), mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 4H), 2.75 (d, J = 6.1 Hz, 2H), 2.81−2.93 (m, 2H), 2.99 (t, J = 6.2 Hz, 2H), 3.18−3.31 (m, 2 H), 3.98−4.15 (m, 2H), 6.37 (d, J = 8.8 Hz, 1H), 6.71 (s, 1H), 6.73−6.82 (m, 2H), 6.91−7.05 (m, 4H), 7.07−7.32 (m, 10H), 7.35 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H). HRMS calcd [$C_{41}H_{39}ClN_2O_6S_2$ + H], 755.201 08; found 755.202 01.

[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]acetaldehyde (46). To a solution of oxalyl chloride (0.37 mL, 4.3 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added DMSO (0.66 mL, 9.3 mmol) dropwise. After 5 min, a solution of 2-{1-benzhydryl-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-5-chloro-1*H*-indol-3-yl}ethanol **36**[44] (2.50 g, 3.9 mmol) in CH_2Cl_2 (8 mL) was added. After 40 min, *i*Pr_2NEt (3.38 mL, 19.4 mmol) was added. The reaction mixture was then subjected to an aqueous workup, and the resulting product was used without further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 0.85 (s, 9 H), 3.11 (t, J = 7.0 Hz, 2 H), 3.58 (t, J = 7.0 Hz, 2 H), 3.71 (d, J = 2.3 Hz, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.68 (dd, J = 8.8, 2.3 Hz, 1 H), 6.87−6.94 (m, 6 H), 7.12−7.20 (m, 10 H), 7.26 (d, J = 7.3 Hz, 2 H), 7.36 (d, J = 2.3 Hz, 4 H), 9.48 (t, J = 2.3 Hz, 1 H).

Methyl 4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}amino)benzoate (47). To a solution of aldehyde **46** (3.9 mmol) in 1,2-dichloroethane (39 mL) at 0 °C were added methyl 4-aminobenzoate (0.65 g, 4.3 mmol), acetic acid (1.33 mL), and $NaBH(OAc)_3$ (2.46 g, 11.6 mmol). The reaction mixture was allowed to warm to room temperature overnight and then subjected to an aqueous workup. The product was used without further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.09 (s, 9 H), 3.21 (t, J = 7.2 Hz, 2 H), 3.32 (t, J = 7.1 Hz, 2 H), 3.57−3.64 (m, 2 H), 3.79 (t, J = 7.2 Hz, 2 H), 3.91 (s, 3 H), 6.66−6.73 (m, 3 H), 6.90 (dd, J = 8.8, 2.27 Hz, 1 H), 7.08−7.14 (m, 5 H), 7.37−7.45 (m, 10 H), 7.49−7.55 (m, 2 H), 7.63−7.68 (m, 4 H), 7.71 (d, J = 2.0 Hz, 1 H), 7.84−7.89 (m, 2 H).

Methyl 4-({2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethyl}amino)benzoate (48). To silyl ether **47** (3.9 mmol) in THF (25 mL) at 0 °C was added a mixture of HOAc/TBAF (1 M in THF) (2.3 mL/5.8 mL), and the reaction mixture was allowed to stir at room temperature for 18 h. Aqueous workup followed by trituration (5% EtOAc/hexanes) afforded **48** (1.64 g, 92% yield, over three steps) as an off-white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 3.00 (t, J = 7.0 Hz, 2 H), 3.31−3.37 (m, 4 H), 3.40 (t, J = 7.2 Hz, 2 H), 3.64 (s, 3 H), 6.41 (d, J = 8.8 Hz, 1 H), 6.51 (d, J = 8.8 Hz, 2 H), 6.62 (dd, J = 8.8, 2.0 Hz, 1 H), 7.03 (dd, J = 7.1, 2.0 Hz, 4 H), 7.11 (s, 1 H), 7.20−7.26 (m, 6 H), 7.45 (d, J = 2.0 Hz, 1 H), 7.61 (d, J = 9.1 Hz, 2 H).

Methyl 4-({2-[2-(2-Azidoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}amino)benzoate (52). To a solution of alcohol **48** (1.64 g, 3.1 mmol) in CH_2Cl_2 at 0 °C were added Et_3N (0.64 mL, 4.6 mmol) and MsCl (0.28 mL, 3.6 mmol). After 30 min, aqueous workup afforded the crude mesylate **51** (1.70 g, 90% yield) as an off-white solid. A solution of the crude mesylate (1.70 g, 2.8 mmol) and NaN_3 (89 mg, 13.8 mmol) in DMF (14 mL) was stirred at 80 °C for 6 h. An aqueous workup followed by flash chromatography (gradient elution 15−25% EtOAc−hexanes) afforded **49** (813 mg, 52% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 2.92−3.01 (m, 4 H), 3.15 (t, J = 7.0 Hz, 2 H), 3.34−3.44 (m, 2 H), 3.60 (s, 3 H), 6.41−6.49 (m, 3 H), 6.64 (dd, J = 8.8, 2.27 Hz, 1 H), 6.93−6.99 (m, 4 H), 7.02 (s, 1 H), 7.15−7.23 (m, 6 H), 7.44 (d, J = 1.5 Hz, 1 H), 7.54−7.60 (m, 2 H).

Methyl 4-({2-[2-(2-Aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}amino)benzoate (53). To a solution of azide **52** (400 mg, 0.7 mmol) in THF (4 mL) at 0 °C was added Ph_3P (223 mg, 0.9 mmol) in portions. The reaction mixture was stirred at room temperature for 11 h and then at 35 °C for 4 h before water (50 uL) was added. The reaction mixture was stirred overnight, and aqueous workup and purification by flash column chromatography (EtOAc to 20% MeOH/EtOAc with 1% Et_3N) afforded **50** (201 mg, 53% yield) as a solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 2.97 (t, J = 7.1 Hz, 2 H), 3.06 (t, J = 6.6 Hz, 2 H), 3.23 (t, J = 6.4 Hz, 2 H), 3.41 (t, J = 7.1 Hz, 2 H), 3.64 (s, 3 H), 6.38 (d, J = 8.8 Hz, 1 H), 6.50 (m, 2 H), 6.60 (dd, J = 8.8, 2.3 Hz, 1 H), 6.93−7.05 (m, 4 H), 7.16−7.27 (m, 6 H), 7.33 (s, 1 H), 7.43 (d, J = 2.3 Hz, 1 H), 7.60 (m, 2 H).

Methyl 4-({2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}amino)benzoate (57). To amine **53** (69 mg, 0.13 mmol) was added α-toluenesulfonyl chloride (30 mg, 0.16 mmol) according to the general Schotten−Baumann procedure. Flash chromatography (gradient elution 20−40% EtOAc−hexanes) afforded **57** (64 mg, 72% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 2.91−3.03 (m, 6 H), 3.37 (q, J = 6.1 Hz, 2 H), 3.64 (s, 3 H), 4.06 (s, 2 H), 6.41 (d, J = 8.8 Hz, 1 H), 6.47−6.51 (m, 2 H), 6.64 (dd, J = 8.8, 2.3 Hz, 1 H), 6.96 (s, 1 H), 6.98−7.04 (m, 4 H), 7.12−7.19 (m, 5 H), 7.20−7.26 (m, 6 H), 7.45 (d, J = 1.8 Hz, 2 H), 7.58−7.64 (m, 2 H).

4-({2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}amino)benzoic Acid (58). Ester **57** (62 mg, 0.1 mmol) was hydrolyzed according to the general procedure to afford **58** (53 mg, 87% yield) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 2.97−3.10 (m, 6 H), 3.45 (t, J = 7.2 Hz, 2 H), 4.15 (s, 2 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.56−6.61 (m, 2 H), 6.72 (dd, J = 8.8, 2.3 Hz, 1 H), 7.05 (s, 1 H), 7.07−7.11 (m, 4 H), 7.20−7.27 (m, 5 H), 7.29−7.36 (m, 6 H), 7.54 (d, J = 2.3 Hz, 1 H), 7.71−7.75 (m, 2 H). HRMS calcd [$C_{39}H_{36}ClN_3O_4S$ + H] 678.218 78; found 678.2178.

Methyl 4-[{2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}(methyl)amino]benzoate (49). To aldehyde **46** [2-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]acetaldehyde (1.50 g, 1.3 mmol) were added methyl 4-(methylamino)benzoate (0.42 g, 2.56 mmol), acetic acid (0.8 mL), and $NaBH(OAc)_3$ (1.48 g, 6.99 mmol) according to the procedure described for **47**. Aqueous workup and purification via flash chromatography (gradient elution 8−20% EtOAc−hexane) generated **49** (1.0 g, 54% yield from alcohol **36**). ^{1}H NMR (400 MHz, acetone-d_6) δ 0.91 (s, 9 H), 2.83 (s, 3 H), 3.05−3.11 (m, 4 H), 3.57 (t, J = 7.0 Hz, 2 H), 3.73 (t, J = 7.0 Hz, 2 H), 3.77 (s, 3 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.60−6.65 (m, 1 H), 6.75 (dd, J = 8.8, 2.3 Hz, 1 H), 6.89 (s, 1 H), 6.92−6.97 (m, 4 H), 7.20−7.28 (m, 11 H), 7.33−7.39 (m, 2 H), 7.43−7.48 (m, 4 H), 7.53 (d, J = 2.0 Hz, 1 H), 7.77 (d, J = 9.1 Hz, 2 H).

Methyl 4-[{2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethyl}(methyl)amino]benzoate (50). To silyl ether **49** (0.99 g, 1.25 mmol) in THF (9 mL) at 0 °C was added a mixture of HOAc/TBAF (1.0 M in THF) (2.3 mL/5.8 mL) according to the procedure used for **48.** The resulting alcohol **49** was used without purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 3.16 (s, 3 H), 3.26 (t, J = 6.7 Hz, 2 H), 3.31 (t, J = 6.7 Hz, 2 H), 3.92 (t, J = 6.4 Hz, 2 H), 3.97−4.00 (m, 2 H), 4.01 (s, 3 H), 6.73 (d, J = 8.8 Hz, 1 H), 6.91−6.98 (m, 3 H), 7.36 (dd, J = 7.2, 2.4 Hz, 4 H), 7.44 (s, 1 H), 7.53−7.60 (m, 7 H), 8.01 (d, J = 9.4 Hz, 2 H).

Methyl 4-[{2-[2-(2-Azidoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}(methyl)amino]benzoate (55). Alcohol **50** (1.20 mmol), Et_3N (0.25 mL, 1.44 mmol), and MsCl (0.11 mL, 1.2 mmol) were reacted using the procedure for **51** to afford the mesylate **54**. The crude mesylate **54** (1.2 mmol) was displaced with NaN_3 (102 mg, 1.56 mmol) as described for **52**. Purifcation by flash chromatography (gradient elution 15–20% EtOAc/hexanes) afforded **55** (426 mg, 61% yield).

Methyl 4-[{2-[2-(2-Aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}(methyl)amino]benzoate (56). A solution of azide **55** (410 mg, 0.71 mmol) and 10% Pd/C (155 mg) in MeOH/CH_2Cl_2 (7 mL/1 mL) was stirred under H_2 atmosphere (1 atm) for 2 h. The reaction mixture was filtered through Celite and rinsed with MeOH and CH_2Cl_2. Flash chromatography (gradient elution with CH_2Cl_2 to 8% MeOH/CH_2Cl_2) gave **56** (305 mg, 78% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 2.92 (s, 3 H), 3.05−3.15 (m, 4 H), 3.28 (t, J = 7.3 Hz, 2 H), 3.77 (s, 3 H), 3.80 (t, J = 6.8 Hz, 2 H), 6.61 (d, J = 8.8 Hz, 1 H), 6.65−6.69 (m, 2 H), 6.80 (dd, J = 8.8, 2.3 Hz, 1 H), 7.11 (dd, J = 7.1, 1.8 Hz, 4 H), 7.15 (s, 1 H), 7.30−7.38 (m, 6 H), 7.56 (d, J = 1.8 Hz, 1 H), 7.75−7.80 (m, 2 H).

4-[{2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}(methyl)amino]benzoic Acid (59). To amine **56** (61 mg, 0.11 mmol) was added α-toluenesulfonyl chloride according to the general Schotten−Baumann procedure. Flash chromatography (20−40% EtOAc/hexanes) afforded **59** (65 mg, 83% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 2.82 (s, 3 H), 2.90−2.99 (m, 6 H), 3.62 (t, J = 6.9 Hz, 2 H), 3.66 (s, 3 H), 4.03 (s, 2 H), 6.42 (d, J = 8.8 Hz, 1 H), 6.50−6.55 (m, 2 H), 6.62−6.68 (m, 1 H), 6.93 (s, 1 H), 6.97−7.02 (m, 4 H), 7.10−7.17 (m, 5 H), 7.21−7.27 (m, 6 H), 7.41 (d, J = 2.0 Hz, 1 H), 7.62−7.68 (m, 2 H).

4-[{2-[2-{2-[(Benzylsulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}(methyl)amino]benzoic Acid (60). Ester **59** (62 mg, 0.09 mmol) was hydrolyzed according to the general procedure to afford **60** (55 mg, 91% yield) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 2.90 (s, 3 H), 2.97−3.06 (m, 6 H), 3.68 (t, J = 6.8 Hz, 2 H), 4.10 (s, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.60 (d, J = 9.3 Hz, 2 H), 6.72 (dd, J = 8.8, 2.0 Hz, 2 H), 7.00 (s, 1 H), 7.04−7.09 (m, 4 H), 7.18−7.24 (m, 5 H), 7.26−7.34 (m, 6 H), 7.48 (d, J = 2.0 Hz, 1 H), 7.73−7.78 (m, 2 H). HRMS calcd [$C_{40}H_{38}ClN_3O_4S$ + H] 692.234 43; found 692.233 74.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-nitrobenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (80). Methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]-ethoxy}benzoate amine **79**[44] (1.0 g, 1.9 mmol) and (2-nitrophenyl)methanesulfonyl chloride (0.43 g, 1.9 mmol) were reacted according to the general Schotten−Baumann procedure. Flash chromatography (gradient elution with 0−1% MeOH in CH_2Cl_2) afforded the sulfonamide **80** (1.13 g, 82% yield) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80−2.98 (m, 2 H), 2.99−3.11 (m, 2 H), 3.19 (t, J = 6.6 Hz, 2 H), 3.88 (s, 3 H), 4.20 (appar t, J = 6.5 Hz, 3 H), 4.64 (s, 2 H), 6.51 (d, J = 9.1 Hz, 1 H), 6.74−6.91 (m, 4 H), 7.00−7.16 (m, 4 H), 7.28−7.38 (m, 6 H), 7.40−7.62 (m, 4 H), 7.88−8.04 (m, 3 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-nitrobenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic acid (81). Ester **80** (1.13 g, 1.50 mmol) was hydrolyzed according to the general procedure to afford **81** (0.95 g, 85% yield) as a pale-yellow foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.02 (s, 4 H), 3.17 (t, J = 6.3 Hz, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.76 (s, 2 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 9.1, 2.2 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.02−7.21 (m, 5 H), 7.29−7.43 (m, 6 H), 7.52 (dd, J = 7.1, 1.9 Hz, 1 H), 7.54−7.72 (m, 4 H), 7.86 (d, J = 8.8 Hz, 2 H), 7.98 (dd, J = 7.3, 2.1 Hz, 1 H). HRMS calcd for [$C_{39}H_{34}ClN_3O_7.S$ + H] 724.1879; found 724.1877.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(3-nitrobenzyl)-sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (82). 3-Nitrophenyl)methanesulfonyl chloride was reacted with amine **79**[44] (0.30 g, 0.57 mmol) using the general Schotten−Baumann procedure. Flash chromatography (20% EtOAc−hexanes) afforded **82** (120 mg, 29% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98−3.06 (m, 2 H), 3.05−3.13 (m, 2 H), 3.17 (t, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 4.23 (t, J = 6.6 Hz, 2 H), 4.52 (s, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.03−7.12 (m, 5 H), 7.31−7.41 (m, 6 H), 7.50 (t, J = 5.2 Hz, 1 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.87 (d, J = 9.1 Hz, 2 H), 8.16−8.25 (m, 2 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(3-nitrobenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (83). Ester **82** (60 mg, 0.20 mmol) was hydrolyzed according to the general procedure to afford **83** (55 mg, 94% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98−3.06 (m, 2 H), 3.05−3.13 (m, 2 H), 3.17 (t, J = 5.8 Hz, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.52 (s, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.6, 2.1 Hz, 1 H), 6.98 (d, J = 9.1 Hz, 2 H), 7.05−7.11 (m, 4 H), 7.31−7.41 (m, 5 H), 7.50 (t, J = 5.6 Hz, 1 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H), 7.74 (d, J = 8.2 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H), 8.16−8.25 (m, 2 H). HRMS calcd for [$C_{39}H_{34}ClN_3O_7S$ + H] 724.1879; found 724.1885.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(4-nitrobenzyl)-sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (84). (4-Nitrophenyl)methanesulfonyl chloride was reacted with amine **79**[44] (0.43 g, 0.80 mmol) using the general Schotten−Baumann procedure. Flash chromatography (20% EtOAc−hexanes) afforded the sulfonamide **84** (150 mg, 25% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.97−3.13 (m, 4 H), 3.18 (t, J = 6.6 Hz, 2 H), 3.80 (s, 3 H), 4.23 (t, J = 6.6 Hz, 2 H), 4.49 (s, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 7.01 (d, J = 8.8 Hz, 2 H), 7.04−7.12 (m, 5 H), 7.32−7.40 (m, 6 H), 7.47−7.58 (m, 3 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.88 (d, J = 9.1 Hz, 2 H), 8.13 (d, J = 8.8 Hz, 2 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(4-nitrobenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (85). Ester **84** (150 mg, 0.2 mmol) was hydrolyzed according to the general procedure to afford the title acid (143 mg, 97% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.96−3.12 (m, 4 H), 3.16 (t, J = 5.8 Hz, 2 H), 4.19 (t, J = 6.9 Hz, 2 H), 4.49 (s, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.8, 1.9 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 2 H), 7.03−7.13 (m, 5 H), 7.30−7.41 (m, 6 H), 7.50−7.63 (m, 3 H), 7.66 (d, J = 1.9 Hz, 1 H), 7.83 (d, J = 8.9 Hz, 2 H), 8.13 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{34}ClN_3O_7S$ + H] 724.1879; found 724.1884.

Methyl 4-{2-[5-Chloro-2-(2-{[(2-cyanobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (86). 2-(Bromomethyl)benzonitrile (3.40 g, 17.4 mmol) was reacted with sodium sulfite as in the general sulfonyl chloride synthesis A to generate (2-cyanophenyl)methanesulfonyl chloride. The crude sulfonyl chloride was reacted with amine **79**[44] (0.085 g, 0.15 mmol) according to the Schotten−Baumann procedure to afford sulfonamide **86** as a gum. ^{1}H NMR (300 Hz, $CDCl_3$) δ 2.95–3.15 (m, 4 H), 3.18 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.34 (s, 2 H), 6.49 (d, J = 8.9 Hz, 1 H), 6.75−6.95 (m, 4 H), 7.05−7.10 (m, 4 H), 7.25−7.35 (m, 6 H), 7.35−7.45 (m, 1 H), 7.45−7.55 (m, 3 H), 7.61 (d, J = 7.6 Hz, 1 H), 7.95 (d, J = 8.9 Hz, 2 H).

4-{2-[1-Benzhydryl-5-chloro-2-(2-{[(2-cyanobenzyl)sulfonyl]-amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (87). Ester **86** was hydrolyzed according to the general procedure to afford **87** (80 mg, 72% overall yield from the amine). ^{1}H NMR (400 Hz, DMSO-d_6) δ 2.95–3.15 (m, 4 H), 3.17 (t, J = 6.5 Hz, 2 H), 4.23 (t, J = 6.5 Hz, 2 H), 4.46 (s, 2 H), 6.47 (d, J = 8.9 Hz, 1 H), 6.81 (dd, J = 8.9, 2.1 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.05−7.10 (m, 6 H), 7.30−7.40 (m, 6 H), 7.50−7.58 (m, 2 H), 7.60−7.70 (m, 3 H), 7.80−7.90 (m, 2 H), 12.60 (br s, 1 H). HRMS calcd [$C_{40}H_{35}ClN_3O_5S$ + H] 704.198 04; found 704.198 39.

Methyl 4-{2-[5-Chloro-2-(2-{[(3-cyanobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (88). 3-Bromomethylbenzamide (3.10 g, 18.3 mmol)) was reacted first with sodium sulfite to yield sodium salt **64** and then with thionyl chloride to generate **70** as in the general sulfonyl chloride synthesis A. The crude sulfonyl chloride was reacted with amine **79**[44] (0.085 g, 0.15 mmol) according to the Schotten−Baumann procedure to afford the sulfonamide **88** as a gum. ^{1}H NMR (300 Hz, $CDCl_3$) δ 2.85−2.95 (m, 2 H), 3.05−3.15 (m, 2 H), 3.15–3.25 (m, 2 H), 3.88 (s, 3 H), 3.95−4.05 (m, 2 H), 4.15−4.30 (m, 2 H), 6.55 (d, J = 9.0 Hz, 1 H), 6.80−6.89 (m, 4 H), 6.90 (s, 1 H), 7.00−7.15 (m, 4 H), 7.25−7.50 (m, 9 H), 7.60 (d, J = 7.2 Hz, 1 H), 7.95 (d, J = 8.2 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(3-cyanobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (89). Ester **88** was hydrolyzed according to the general procedure to afford the title acid (90 mg, 81% overall yield from the amine) as a white solid. ^{1}H NMR (400 Hz, DMSO-d_6) δ 2.95−3.10 (m, 4 H), 3.17 (t, J = 6.5 Hz, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.39 (s, 2 H), 6.47 (d, J = 8.9 Hz, 1 H), 6.81 (dd, J = 8.9, 2.2 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.05–7.15 (m, 6 H), 7.30−7.40 (m, 6 H), 7.50 (t, J = 5.9 Hz, 1 H), 7.61 (d, J = 7.9 Hz, 1 H), 7.66 (d, J = 2.1 Hz, 1 H), 7.74 (s, 1 H), 7.79 (d, J = 7.7 Hz, 1 H), 7.90 (d, J = 8.8 Hz, 2 H), 12.60 (br s, 1 H). HRMS calcd [$C_{40}H_{33}ClN_3O_5S$ – H] 702.1834; found 702.1833. Anal. ($C_{40}H_{34}ClN_3O_5S \cdot 0.7H_2O$) C, H, N.

Methyl 4-{2-[5-Chloro-2-(2-{[(4-cyanobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (90). 4-(Bromomethyl)benzonitrile (9.80 g, 50 mmol) was reacted with sodium sulfite as in the general sulfonyl chloride synthesis A to generate (4-cyanophenyl)methanesulfonyl chloride **71**. The crude sulfonyl chloride was reacted with methyl 4-(2-(2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl)ethoxy)benzoate amine **79**[44] (0.085 g, 0.15 mmol) according to the Schotten−Baumann procedure to afford sulfonamide **90** as a gum. ^{1}H NMR (300 Hz, $CDCl_3$) δ 2.82−2.92 (m, 2 H), 3.10 (t, J = 6.9 Hz, 2 H), 3.19 (t, J = 6.4 Hz, 2 H), 3.88 (s, 3 H), 4.00−4.05 (m, 2 H), 4.22 (t, J = 6.2 Hz, 2 H), 4.30 (t, J = 6.3 Hz, 1 H), 6.52 (d, J = 8.9 Hz, 1 H), 6.75−6.95 (m, 4 H), 7.05−7.10 (m, 4 H), 7.20−7.35 (m, 8 H), 7.55−7.65 (m, 3 H), 7.94 (d, J = 8.9 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(4-cyanobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic acid (91). Ester **90** was hydrolyzed according to the general procedure to afford the title acid (84 mg, 77% overall yield from the amine) as an off-white solid. ^{1}H NMR (400 Hz, DMSO-d_6) δ 2.95−3.15 (m, 4 H), 3.17 (t, J = 6.5 Hz, 2 H), 4.23 (t, J = 6.5 Hz, 2 H), 4.41 (s, 2 H), 6.46 (d, J = 8.9 Hz, 1 H), 6.81 (dd, J = 8.9, 2.2 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.05−7.15 (m, 6 H), 7.30−7.40 (m, 6 H), 7.46 (d, J = 8.3 Hz, 2 H), 7.66 (d, J = 2.1 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 2 H), 7.85 (d, J = 8.8 Hz, 2 H), 12.60 (br s, 1 H). HRMS calcd [$C_{40}H_{35}ClN_3O_5S$ + H] 704.1980; found 704.1981. Anal. ($C_{40}H_{34}ClN_3O_5S$) C, H, N.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(pyridin-2-ylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (92). This compound was prepared by stirring amine **79**[44] (300 mg, 0.56 mmol), 2-(pyridylmethyl)sulfonyl chloride·TFA (230 mg, 0.68 mmol), and DIEA (0.2 mL, 1.1 mmol) in CH_2Cl_2 (6 mL) for 2 h. The mixture was then subjected to an aqueous workup and purified by flash chromatography (50% EtOAc−hexanes) to afford the sulfonamide **92** (163 mg, 42% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 4 H), 3.23 (t, J = 6.6 Hz, 2 H), 3.88 (s, 3 H), 4.18−4.32 (m, 4 H), 4.81 (s, 1 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.76−6.91 (m, 3 H), 6.95 (s, 1 H), 7.02−7.12 (m, 4 H), 7.18 (dd, J = 7.1, 5.2 Hz, 1 H), 7.21−7.40 (m, 7 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.63 (dt, J = 7.7, 1.7 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H), 8.26 (d, J = 4.1 Hz, 1 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(pyridin-2-ylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic acid (93). Ester **92** (163 mg, 0.23 mmol) was hydrolyzed according to the general procedure to afford **93** (90 mg, 56% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.92−3.25 (m, 6 H), 4.22 (t, J =

6.7 Hz, 2 H), 4.43 (s, 2 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.04−7.19 (m, 5 H), 7.26−7.53 (m, 9 H), 7.66 (d, J = 1.9 Hz, 1 H), 7.73 (dt, J = 7.7, 1.9 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H), 8.44 (d, J = 4.9 Hz, 1 H). HRMS calcd [$C_{38}H_{34}Cl_1N_3O_5S_1$ − H] 678.183 49; found 678.183 12.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(pyridin-3-ylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (94). This compound was prepared by reacting amine **79**[44] (150 mg, 0.28 mmol) with 3-(pyridylmethyl)sulfonyl chloride·TFA (115 mg, 0.34 mmol) using the DIEA procedure described for **92**. Aqueous workup and flash chromatography (2% MeOH−CH_2Cl_2) afforded the sulfonamide **94** (100 mg, 52% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (q, J = 7.1 Hz, 2 H), 3.03−3.15 (m, 2 H), 3.19 (t, J = 6.6 Hz, 2 H), 3.88 (s, 3 H), 4.01 (s, 2 H), 4.22 (t, J = 6.6 Hz, 2 H), 4.54 (t, J = 6.0 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.74−6.88 (m, 3 H), 6.91 (s, 1 H), 7.00−7.14 (m, 4 H), 7.22 (dd, J = 8.1, 5.1 Hz, 1 H), 7.28−7.39 (m, 6 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H), 8.39 (s, 1 H), 8.52 (d, J = 4.4 Hz, 1 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(pyridin-3-ylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (95). Ester **94** (100 mg, 0.14 mmol) was hydrolyzed according to the general procedure to afford **95** (92 mg, 94% yield) as a yellow foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.85−3.25 (m, 6 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.35 (s, 2 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.82 (d, J = 1.9 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.09 (appar dd, J = 5.2, 2.2 Hz, 5 H), 7.25−7.44 (m, 7 H), 7.50 (t, J = 5.5 Hz, 1 H), 7.61−7.75 (m, 2 H), 7.86 (d, J = 9.1 Hz, 2 H), 8.42−8.56 (m, 2 H). HRMS calcd [$C_{38}H_{34}Cl_1N_3O_5S_1$ − H] 678.183 49; found 678.182 77.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(pyridin-4-ylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (96). This compound was prepared using methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate **79**[44] (150 mg, 0.28 mmol) and 4-(pyridylmethyl)sulfonyl chloride·TFA (115 mg, 0.34 mmol) using the DIEA procedure described for **92**. Aqueous workup and purification by flash chromatography (2% MeOH−CH_2Cl_2) afforded the sulfonamide **96** (110 mg, 57% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (q, J = 7.2 Hz, 2 H), 3.04−3.38 (m, 4 H), 3.88 (s, 3 H), 3.98 (s, 2 H), 4.23 (t, J = 6.5 Hz, 2 H), 4.63 (t, J = 5.9 Hz, 1 H), 6.54 (d, J = 9.1 Hz, 1 H), 6.84 (d, J = 9.1 Hz, 3 H), 6.91 (s, 1 H), 7.02−7.19 (m, 6 H), 7.28−7.43 (m, 6 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 9.1 Hz, 2 H), 8.46 (d, J = 5.8 Hz, 2 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(pyridin-4-ylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (97). Ester **96** (110 mg, 0.16 mmol) was hydrolyzed according to the general procedure to afford acid **97** (111 mg, 94% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.93−3.24 (m, 6 H), 4.22 (t, J = 6.6 Hz, 2 H), 4.35 (s, 2 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.4, 1.8 Hz, 1 H), 6.98 (d, J = 9.1 Hz, 2 H), 7.04−7.19 (m, 5 H), 7.27 (d, J = 5.8 Hz, 2 H), 7.32−7.44 (m, 6 H), 7.53 (t, J = 5.1 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.86 (d, J = 8.5 Hz, 2 H), 8.48 (d, J = 5.8 Hz, 2 H). HRMS calcd [$C_{38}H_{34}Cl_1N_3O_5S_1$ − H] 678.183 49; found 678.182 49.

Methyl 4-{2-[5-Chloro-2-(2-{[(cyclohexylmethyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (98). Cyclohexylmethanesulfonyl chloride was reacted with **79**[44] (0.25 g, 0.46 mmol) according to the Schotten−Baumann procedure and afforded sulfonamide **98** (64 mg, 20% yield) as a pale-yellow foam after purification by flash chromatography (gradient elution 20−50% EtOAc−hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60−1.43 (m, 7 H), 1.58−1.89 (m, 4 H), 2.61 (d, J = 5.8 Hz, 2 H), 2.90−3.09 (m, 2 H), 3.10−3.35 (m, 4 H), 3.88 (s, 3 H), 4.14 (t, J = 6.9 Hz, 1 H), 4.25 (t, J = 6.5 Hz, 2 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.75−6.91 (m, 3 H), 6.95 (s, 1 H), 7.09 (dd, J = 3.4, 2.6 Hz, 4 H), 7.28−7.48 (m, 6 H), 7.56 (d, J = 2.2 Hz, 1 H), 7.96 (d, J = 8.5 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(cyclohexylmethyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (99). Ester **98** (64 mg, 0.091 mmol) was hydrolyzed according to the general procedure to afford the title acid (46 mg, 73% yield) as an off-white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.65−1.35 (m, 6 H), 1.46−1.81 (m, 5 H), 2.71 (d, J = 5.5 Hz, 2 H), 3.06 (s, 4 H), 3.20 (t, J = 5.4 Hz, 2 H), 4.11−4.37 (m, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.2 Hz, 1 H), 6.98 (d, J = 9.1 Hz, 2 H), 7.10 (dd, J = 7.4, 1.9 Hz, 5 H), 7.25−7.52 (m, 7 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H). HRMS calcd [$C_{39}H_{41}Cl_1N_2O_5S_1$ − H] 683.235 19; found 683.23474.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-naphthylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (100). 2-(Bromomethyl)naphthalene (1.6 g, 7.4 mmol) was reacted with sodium sulfite as in the general sulfonyl chloride synthesis A to generate 2-naphthylmethanesulfonyl chloride **72**. The crude sulfonyl chloride was reacted with amine **79**[44] (0.17 g, 0.32 mmol) according to the Schotten−Baumann procedure. Flash chromatography (10−40% EtOAc−hexanes) afforded the sulfonamide **100** (140 mg, 58% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80−2.98 (m, 2 H), 2.99−3.24 (m, 4 H), 3.88 (s, 3 H), 4.05−4.18 (m, 3 H), 4.20 (s, 2 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.70−6.85 (m, 3 H), 6.88 (s, 1 H), 6.98−7.12 (m, 4 H), 7.19−7.36 (m, 7 H), 7.43−7.56 (m, 3 H), 7.63 (s, 1 H), 7.65−7.75 (m, 2 H), 7.76−7.85 (m, 1 H), 7.91 (d, J = 9.1 Hz, 2 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-naphthylmethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (101). Ester **100** (137 mg, 0.18 mmol) was hydrolyzed according to the general procedure to afford **101** (100 mg, 75% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.87−3.25 (m, 6 H), 4.19 (t, J = 6.7 Hz, 2 H), 4.44 (s, 2 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.2 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.03−7.20 (m, 5 H), 7.28−7.45 (m, 8 H), 7.46−7.56 (m, 2 H), 7.66 (d, J = 1.9 Hz, 1 H), 7.73−7.97 (m, 6 H). HRMS calcd for [$C_{43}H_{37}ClN_2O_5S$ + H] 729.2185; found 729.2189.

Methyl 4-{2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (102). To amine **79**[44] (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 **102** (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 (d, J = 8.8 Hz, 1 H), 6.78−6.93 (m, 4 H), 7.02−7.12 (m, 4 H), 7.16 – 7.38 (m, 9 H), 7.41 (d, J = 7.4 Hz, 1 H), 7.53 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (103). Ester **102** (250 mg, 0.34 mmol) was hydrolyzed according to the general procedure to afford acid **103** (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.

Methyl 4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-methylbenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (104). 2-Methylphenylmethanesulfonyl chloride was reacted with amine **79**[44] (0.116 g, 0.17 mmol) according to the Schotten−Baumann procedure. Flash chromatography (gradient elution EtOAc−hexanes) afforded the sulfonamide **104** (0.049 g, 35% yield) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.12 (s, 3 H), 2.63−2.73 (m, 2 H), 2.84−2.94 (m, 2 H), 2.97−3.05 (m, 2 H), 3.71 (s, 3 H), 3.96 (s, 2 H), 3.97−4.06 (m, 2 H), 6.34 (d, J = 9.1 Hz, 1 H), 6.61−6.69 (m, 3 H), 6.72 (s, 1 H), 6.85−6.92 (m, 6 H), 6.93−7.05 (m, 2 H), 7.10−7.19 (m, 6 H), 7.36 (d, J = 1.9 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 2 H).

4-{2-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-methylbenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (105). Ester **104** (0.046 g, 0.07 mmol) was hydrolyzed according to the general procedure to afford acid **105** (0.031 g, 69% yield) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.13 (s, 3 H), 2.62−2.74 (m,

2 H), 2.83−2.94 (m, 2 H), 2.95−3.06 (m, 2 H), 3.96 (s, 2 H), 4.02 (t, J = 6.9 Hz, 2 H), 6.34 (d, J = 8.5 Hz, 1 H), 6.59−6.70 (m, 3 H), 6.72 (s, 1 H), 6.84−6.93 (m, 6 H), 7.11−7.19 (m, 8 H), 7.35 (s, 1 H), 7.82 (d, J = 8.2 Hz, 2 H). HRMS calcd for [$C_{401}H_{37}ClN_2O_5S$ − H] 691.203 89; found 691.203 50.

2,6-Dimethylphenylmethanesulfonyl Chloride (77). This compound was synthesized using sulfonyl chloride general procedure C. 2-Chloromethyl-1,3-dimethylbenzene (10 g, 64.7 mmol) was treated as in the general procedure to yield the desired sulfonate sodium salt (11.92 g, 83%). This material was treated with HCl (90% yield of **74**) and chlorinated (92% yield of **77**) as described in the general procedure to yield sulfonyl chloride **77**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.50 (s, 6 H), 5.17 (s, 2 H), 7.25–7.04 (m, 3 H).

Methyl 4-{2-[5-Chloro-2-(2-{[(2,6-dimethylbenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (106). To amine **79**[44] (114 mg, 0.212 mmol) was added 2,6-dimethylphenylmethanesulfonyl chloride **77** using the Schotten−Baumann general procedure. Flash chromatography afforded the sulfonamide **106** (0.069 g, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.11 (s, 6 H), 2.61−2.72 (m, 2 H), 2.82−2.92 (m, 2 H), 2.96−3.06 (m, 2 H), 3.71 (s, 3 H), 3.98−4.07 (m, 3 H), 4.13 (s, 2 H), 6.34 (d, J = 8.8 Hz, 1 H), 6.61−6.73 (m, 4 H), 6.78 (s, 1 H), 6.81 (s, 1 H), 6.85−6.95 (m, 5 H), 7.10−7.18 (m, 6 H), 7.36 (d, J = 1.9 Hz, 2 H), 7.79 (d, J = 8.8 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(2,6-dimethylbenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (107). Ester **106** (0.064 g, 0.089 mmol) was hydrolyzed according to the general procedure to afford the acid **107** (0.056 g, 88% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.10 (s, 6 H), 2.87 (br s, 4 H), 2.94−3.02 (m, 2 H), 3.96−4.04 (m, 2 H), 4.13−4.19 (m, 2 H), 6.28 (d, J = 8.8 Hz, 2 H), 6.62 (dd, J = 8.7, 2.3 Hz, 2 H), 6.71 (d, J = 8.8 Hz, 2 H), 6.78 (s, 1 H), 6.80 (s, 1 H), 6.84−6.93 (m, 5 H), 7.12−7.22 (m, 5 H), 7.40−7.46 (m, 1 H), 7.47 (d, J = 1.6 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{41}H_{39}Cl_1N_2O_5S_1$ + H] 707.2341; found 707.234 54.

Methyl 4-{2-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (108). 2-(Bromomethyl)-1,3-difluorobenzene (20 g, 96.6 mmol) was reacted with sodium sulfite as in the general sulfonyl chloride synthesis C to generate (2,6-difluorophenyl)methanesulfonyl chloride **78**. The crude sulfonyl chloride was reacted with amine **79**[44] (2.0 g, 3.71 mmol) according to the Schotten−Baumann procedure. Flash chromatography (gradient elution 10−30% EtOAc−hexanes) afforded the sulfonamide **108** (2.65 g, 98% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.96−3.24 (m, 6 H), 3.80 (s, 3 H), 4.24 (t, J = 6.5 Hz, 2 H), 4.32 (s, 2 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.9, 2.1 Hz, 1 H), 7.01 (d, J = 9.1 Hz, 2 H), 7.05−7.16 (m, 7 H), 7.29−7.52 (m, 7 H), 7.67 (d, J = 2.2 Hz, 1 H), 7.73 (t, J = 5.2 Hz, 1 H), 7.88 (d, J = 9.1 Hz, 2 H).

4-{2-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (109). Ester **108** (2.5 g, 3.43 mmol) was hydrolyzed according to the general procedure to afford acid **109** (2.11 mg, 86% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.97−3.26 (m, 6 H), 4.23 (t, J = 6.6 Hz, 2 H), 4.32 (s, 2 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.76−6.84 (m, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.04−7.17 (m, 7 H), 7.30−7.52 (m, 7 H), 7.67 (d, J = 1.4 Hz, 1 H), 7.75 (t, J = 5.5 Hz, 1 H), 7.86 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}ClF_2N_2O_5S$ − H] 713.169 40; found 713.169 06.

Methyl 4-{3-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (110). This compound was prepared from amine **22** (0.43 g, 0.80 mmol) and (3,4-dichlorophenyl)methanesulfonyl chloride (0.22 g, 0.83 mmol) according to the Schotten−Baumann procedure and purified using flash chromatography (gradient elution with 2:1 EtOAc in hexanes, then 10% MeOH CH_2Cl_2) to afford the sulfonamide **110** (0.47 g, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87−2.04 (m, 2 H), 2.69−2.83 (m, 6 H), 2.92−3.00 (m, 2 H), 3.90 (s, 3 H), 3.93 (s, 2 H), 4.03 (t, J = 6.2 Hz, 1 H), 6.52 (dd, J = 8.8 Hz, 1 H), 7.00 (dd, J = 8.1, 2.1 Hz, 1 H), 7.05−7.11 (m, 4 H), 7.25 (s, 1 H), 7.26−7.28 (m, 3 H), 7.29−7.31 (m, 2 H), 7.31−7.36 (m, 6 H), 7.43 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 8.2 Hz, 2 H)

4-{3-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (111). Ester **110** (0.45 g, 0.61 mmol) was hydrolyzed according to the general procedure to afford **111** (0.39 g, 86% yield), mp 172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92−2.04 (m, 2 H), 2.70−2.85 (m, 6 H), 2.93−3.02 (m, 2 H), 3.94 (s, 2 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.82 (dd, J = 8.8, 2.2 Hz, 1 H), 6.87 (s, 1 H), 7.00 (dd, J = 8.2, 1.9 Hz, 1 H), 7.05−7.11 (m, 4 H), 7.26−7.28 (m, 2 H), 7.30 (d, J = 2.7 Hz, 2 H), 7.31−7.37 (m, 6 H), 7.42 (d, J = 1.9 Hz, 1 H), 8.01 (d, J = 8.2 Hz, 2 H). Anal. ($C_{40}H_{35}Cl_3N_2O_4S$) C, H, N. HRMS calc for [$C_{40}H_{35}Cl_3N_2O_4S$ + H] 745.1456; found 745.1458.

Methyl 4-({2-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}-sulfonyl)benzoate (112). This compound was prepared from amine **33** (0.15 g, 0.23 mmol) and (3,4-dichlorophenyl)methanesulfonyl chloride (0.14 g, 0.54 mmol) according to the Schotten−Baumann procedure and purified using flash chromatography (EtOAc−hexanes) to afford sulfonamide **112** (0.18 g, 87% yield) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 3.10−3.30 (m, 6 H), 3.60−3.67 (m, 2 H), 3.96 (s, 3 H), 4.33 (s, 2 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.77 (dd, J = 8.8, 2.0 Hz, 1 H), 7.11−7.18 (m, 5 H), 7.27 (d, J = 2.3 Hz, 1 H), 7.33 (dd, J = 8.2, 1.9 Hz, 1 H), 7.35−7.40 (m, 6 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.59 (d, J = 2.0 Hz, 1 H), 8.12−8.17 (m, 2 H), 8.22−8.28 (m, 2 H).

4-({2-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoic Acid (113). Ester **112** (0.15 g, 0.19 mmol) was hydrolyzed according to the general procedure to afford **113** (0.14 g, 93% yield) as a pale-yellow solid; mp 94.8, 129.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85−2.97 (m, 2H), 2.98−3.09 (m, 2H), 3.16−3.29 (m, J = 2.8 Hz, 2H), 3.37−3.50 (m, 2H), 4.01 (s, 2H), 4.39 (t, J = 6.2 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 6.71−6.82 (m, 2H), 6.82−6.86 (m, 1H), 7.02−7.12 (m, 6H), 7.23 (s, 1H), 7.28−7.41 (m, 6H), 8.06 (d, J = 8.3 Hz, 2H), 8.26 (d, J = 8.31 Hz, 2H). HRMS: calcd for [$C_{39}H_{33}Cl_3N_2O_6S_2$ – H] 793.077 28; found 793.076 29.

Methyl 4-{3-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate(114). 1-(Bromomethyl)-2-chlorobenzene (5.0 g, 31.0 mmol) was reacted with PCl_5 (15.0 g, 73 mmol over two additions) to generate (2-chlorophenyl)methanesulfonyl chloride. The crude sulfonyl chloride was dissolved in CH_2Cl_2, and the mixture was cooled to 0 °C. Then amine **22** (6.2 g, 11.5 mmol) was added in one portion, followed by DIEA (4.0 mL, 23 mmol). The mixture was warmed to room temperature over 4 h. An aqueous workup was performed and flash chromatography (30% EtOAc−hexanes) afforded the sulfonamide **114** (7.89 g, 94% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−1.98 (m, 2 H), 2.63−2.74 (m, 4 H), 2.74−2.84 (m, 2 H), 2.83−2.95 (m, 2 H), 3.87 (s, 3 H), 4.29 (s, 2 H), 6.45 (d, J = 9.1 Hz, 1 H), 6.76 (dd, J = 8.9, 2.1 Hz, 1 H), 6.82 (s, 1 H), 7.02 (dd, J = 5.8, 3.6 Hz, 4 H), 7.18−7.22 (m, 2 H), 7.25−7.32 (m, 8 H), 7.34−7.41 (m, 2 H), 7.92 (d, J = 8.2 Hz, 2 H).

4-{3-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (115). Ester **114** (7.89 g, 10.9 mmol) was hydrolyzed according to the general procedure to afford the acid **115** (6.4 g, 83% yield) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84−1.98 (m, 2 H), 2.70 (m, 4 H), 2.76−2.86 (m, 2 H), 2.86−2.98 (m, J = 7.4 Hz, 2 H), 4.30 (s, 2 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.8, 1.9 Hz, 1 H), 6.82 (s, 1 H), 7.00−7.07 (m, 4 H), 7.11−7.21 (m, 2 H), 7.22−7.25 (m, 2 H), 7.25−7.32 (m, 7 H), 7.33−7.39 (m, 2 H), 7.98 (d, J = 8.0 Hz, 2 H). HRMS calcd for [$C_{40}H_{36}Cl_2N_2O_4S$ − H] 709.170 00; found 709.169 61.

Methyl 4-({2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (116). To amine **33** (0.153 mg, 0.26 mmol) was added (2-chlorophenyl-)methanesulfonyl chloride (0.200 g, 0.89 mmol) (see prep in **114**), using the Schotten−Baumann general procedure to generate the sulfonamide **116** (0.08 g, 40% yield) after purification by preparative TLC (3% MeOH in CH_2Cl_2).

4-({2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoic Acid (117). Ester **116** (0.08 g, 0.103 mmol) was hydrolyzed according to the general procedure to afford the acid **117** (0.063 g, 80% yield) as an orange solid, mp 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89−3.01 (m, 4 H), 3.12−3.21 (m, 2 H), 3.37−3.45 (m, 2 H), 4.36 (s, 2 H), 4.52 (t, J = 5.8 Hz, 1 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.77 (dd, J = 9.1, 2.1 Hz, 1 H), 6.81 (s, 1 H), 7.01−7.07 (m, 4 H), 7.19 (d, J = 2.01 Hz, 1 H), 7.21−7.24 (m, 1 H), 7.27−7.32 (m, 7 H), 7.33−7.37 (m, 1 H), 7.39−7.45 (m, 1 H), 8.05 (d, J = 7.9 Hz, 2 H), 8.26 (d, J = 7.93 Hz, 2 H). HRMS calcd for [$C_{39}H_{34}Cl_2N_2O_6S_2$ + H] 761.130 81; found 761.131 46.

Methyl 4-{3-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-methylbenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]propyl}benzoate (118). This compound was prepared using amine **22** (0.540 g, 10.0 mmol) and [(2-methylphenyl)methane]sulfonyl chloride (15 mmol) using the above DIEA procedure. Flash chromatography (5–20% EtOAc−hexanes) afforded the sulfonamide **118** (6.17 g, 88% yield) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86−2.00 (m, 2 H), 2.30 (s, 3 H), 2.62−2.83 (m, 6 H), 2.84−3.02 (m, 2 H), 3.89 (s, 3 H), 4.06−4.18 (m, 3 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.75−6.83 (m, J = 8.8, 2.0 Hz, 1 H), 6.84 (s, 1 H), 7.00−7.09 (m, 6 H), 7.09−7.14 (m, 1 H), 7.15−7.21 (m, 1 H), 7.22−7.28 (m, 2 H), 7.28−7.35 (m, 6 H), 7.40 (d, J = 2.0 Hz, 1 H), 7.95 (d, J = 8.1 Hz, 2 H).

4-{3-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-methylbenzyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (119). Ester **118** (6.0 g, 8.5 mmol) was hydrolyzed according to the general procedure to afford acid **119** (5.03 g, 86% yield) as a yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80−1.95 (m, 2 H), 2.28 (s, 3 H), 2.71 (t, J = 7.6 Hz, 4 H), 2.92 (br s, 4 H), 4.27 (s, 2 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.77 (dd, J = 8.8, 2.3 Hz, 1 H), 6.99−7.12 (m, 6 H), 7.12−7.25 (m, 3 H), 7.28−7.44 (m, 9 H), 7.46 (d, J = 2.0 Hz, 1 H), 7.86 (d, J = 8.3 Hz, 2 H), 12.76 (br s, 1 H). HRMS calcd for [$C_{41}H_{39}ClN_2O_4S$ + H] 691.239 18; found 691.239 46. Anal. ($C_{41}H_{39}ClN_2O_4S$) C, H, N.

Methyl 4-{3-[5-Chloro-2-(2-{[(2,6-dimethylbenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (120). This compound was prepared by reacting amine **22** (4.40 g, 8.3 mmol) with (2,6-dimethylphenyl)methanesulfonyl chloride **77** (2.67 g, 12.0 mmol) using the DIEA procedure described for **92**. Aqueous workup and purification by flash chromatography (gradient elution 5–30% EtOAc−hexanes) afforded the sulfonamide **120** (4.82 g, 81% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87−2.01 (m, 2 H), 2.31 (s, 6 H), 2.65−2.82 (m, 6 H), 2.88−2.97 (m, 2 H), 3.90 (s, 3 H), 4.04 (t, J = 6.2 Hz, 1 H), 4.28 (s, 2 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.3 Hz, 1 H), 6.83 (s, 1 H), 6.96 (appar d, J = 7.3 Hz, 2 H), 7.02−7.08 (m, 5 H), 7.21−7.28 (m, 3 H), 7.29−7.36 (m, 5 H), 7.40 (d, J = 2.3 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 2 H).

4-{3-[5-Chloro-2-(2-{[(2,6-dimethylbenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (121). Ester **120** (0.81 g, 1.1 mmol) was hydrolyzed according to the general procedure to afford acid **121** (0.73 g, 93% yield) as a white foam, mp 194–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81−1.95 (m, 2 H), 2.30 (s, 6 H), 2.68−2.79 (m, 4 H), 2.87−3.08 (m, 4 H), 4.34 (s, 2 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.78 (dd, J = 8.8, 2.0 Hz, 1 H), 6.98 (appar d, J = 7.1 Hz, 2 H), 7.03−7.14 (m, 6 H), 7.25−7.41 (m, 8 H), 7.46 (d, J = 2.3 Hz, 1 H), 7.51 (t, J = 5.3 Hz, 1 H), 7.85 (d, J = 8.1 Hz, 2 H). HRMS calcd for $C_{42}H_{41}ClN_2O_4S$ + H] 705.254 83; found 705.254 86. Anal. ($C_{42}H_{41}ClN_2O_4S$) C, H, N.

Methyl 4-({2-[5-Chloro-2-(2-{[(2,6-dimethylbenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (122). This compound was prepared by reacting amine **33** (0.51 g, 0.87 mmol) with (2,6-dimethylphenyl)methanesulfonyl chloride **77** (0.58 g, 2.63 mmol) using the Schotten−Baumann general procedure and flash chromatography (1% MeOH/CH_2Cl_2) to afford the sulfonamide **122** (0.54 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 6 H), 2.88 (t, J = 6.7 Hz, 2 H), 2.95 (d, J = 7.1 Hz, 2 H), 3.14−3.20 (m, 2 H), 3.37−3.45 (m, 2 H), 3.97 (s, 3 H), 4.33 (s, 2 H), 4.39 (t, J = 6.2 Hz, 1 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.77 (dd, J = 8.9, 2.1 Hz, 1 H), 6.81 (s, 1 H), 6.96−7.12 (m, 7 H), 7.19 (d, J = 2.0 Hz, 1 H), 7.27−7.34 (m, 6 H), 8.03 (d, J = 8.6 Hz, 2 H), 8.21 (d, J = 8.6 Hz, 2 H).

4-({2-[5-Chloro-2-(2-{[(2,6-dimethylbenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoic Acid (123). Ester **122** (0.56 g, 0.73 mmol) was hydrolyzed according to the general procedure to afford the acid **123** (0.55 g, 99% yield) as a white solid, mp 144.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 6 H), 2.86−2.91 (m, 2 H), 2.92−3.00 (m, 2 H), 3.14−3.22 (m, 2 H), 3.39−3.47 (m, 2 H), 4.32−4.36 (m, 2 H), 4.61 (t, J = 6.2 Hz, 1 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.77 (dd, J = 8.8, 2.1 Hz, 1 H), 6.80 (s, 1 H), 6.96−7.11 (m, 7 H), 7.18 (d, J = 2.01 Hz, 1 H), 7.27−7.35 (m, 6 H), 8.05 (d, J = 8.3 Hz, 2 H), 8.23 (d, J = 8.3 Hz, 2 H). HRMS calcd for [$C_{41}H_{39}ClN_2O_6S_2$ – H] 753.186 53 found 753.185 97.

Methyl 4-{3-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (124). To amine **22** (400 mg, 7.4 mmol) was added (2,6-difluorophenyl-)methanesulfonyl chloride **78** using the Schotten−Baumann general procedure and flash chromatography (20% EtOAc−hexanes) to afford sulfonamide **124** (180 mg, 33% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−2.03 (m, 2 H), 2.61−2.80 (m, 4 H), 2.85−3.05 (m, 4 H), 3.90 (s, 3 H), 4.03−4.15 (m, 1 H), 4.22 (d, 2 H), 6.49 (d, J = 8.5 Hz, 1 H), 6.71−6.95 (m, 4 H), 6.98−7.15 (m, 4 H), 7.19−7.37 (m, 9 H), 7.41 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 8.5 Hz, 2 H).

4-{3-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (125). Ester **124** (180 mg, 0.25 mmol) was hydrolyzed according to the general procedure to afford acid **125** (46 mg, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−2.03 (m, 2 H), 2.59−2.85 (m, 4 H), 2.84−3.08 (m, 4 H), 4.18−4.26 (m, 2 H), 4.25−4.32 (m, 1 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.66−6.94 (m, 4 H), 7.08 (s, 4 H), 7.19−7.39 (m, 9 H), 7.42 (s, 1 H), 8.00 (d, J = 8.2 Hz, 2 H). HRMS calcd for [$C_{40}H_{35}ClF_2N_2O_4S$ − H] 711.190 13; found 711.189 65.

Methyl 4-({2-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoate (126). To amine **33** (0.157 g, 0.27 mmol) was added (2,6-difluorophenyl)methanesulfonyl chloride **78** (0.21 g, 0.91 mmol) using the Schotten−Baumann general procedure and flash chromatography (3% MeOH/CH_2Cl_2) to afford sulfonamide **126** (0.14 g, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98−3.08 (m, 4 H), 3.15−3.24 (m, 2 H), 3.37−3.45 (m, 2 H), 3.97 (s, 3 H), 4.26 (s, 2 H), 4.51 (t, J = 5.8 Hz, 1 H), 6.45 (d, J = 8.8 Hz, 1 H), 6.78 (dd, J = 8.8, 2.0 Hz, 1 H), 6.85 (s, 1 H), 6.87−6.96 (m, 2 H), 7.05 (dd, J = 5.7, 3.7 Hz, 4 H), 7.21 (d, J = 2.0 Hz, 1 H), 7.27−7.35 (m, 7 H), 8.02 (d, J = 8.6 Hz, 2 H), 8.22 (d, J = 8.8 Hz, 2 H)

4-({2-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)benzoic Acid (127). Ester **126** (0.14 g, 0.18 mmol) was hydrolyzed according to the general procedure to afford acid **127** (0.13 g, 96% yield) as a pale-yellow solid, mp 124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97−3.10 (m, 4 H), 3.14−3.24 (m, 2 H), 3.37−3.49 (m, 2 H), 4.27 (s, 2 H), 4.77 (t, J = 5.8 Hz, 1 H), 6.45 (d, J = 8.0 Hz, 1 H), 6.74−6.80 (m, 1 H), 6.85 (s, 1 H), 6.86−6.94 (m, 2 H), 7.06 (dd, J = 5.7, 3.4 Hz, 4 H), 7.20 (t, J = 2.1 Hz, 1 H), 7.27−7.34 (m, 7 H), 8.04 (d, J = 8.3 Hz, 2 H), 8.22 (d, J = 8.3 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}ClF_2N_2O_6S_2$ − H] 761.136 38; found 761.135 65.

Methyl 3-[4-({2-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)-phenyl]propanoate (135). This compound was prepared from amine **43** (0.130 g, 0.21 mmol) and (3,4-dichlorophenyl)methanesulfonyl chloride (0.061 g, 0.23 mmol) according to the Schotten−Baumann procedure and purified using flash chromatography (EtOAc−hexanes) to afford sulfonamide **135** (0.150 g, 85% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (t, J = 7.6 Hz, 2 H), 2.88−3.01 (m, 4 H), 3.05 (t, J = 7.6 Hz, 2 H), 3.11−3.18 (m, 2 H), 3.33−3.40 (m, 2 H), 3.66 (s, 3 H), 4.00 (s, 2 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.72 (dd, J = 7.3, 1.8 Hz, 1 H), 6.79 (dd, J = 8.8, 2.0 Hz, 1 H), 6.83 (d, J = 7.3 Hz, 1 H), 6.86 (s, 1 H), 7.02−7.09 (m, 4 H),

7.20−7.22 (m, 1 H), 7.28−7.33 (m, 5 H), 7.33−7.36 (m, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 7.86 (d, J = 8.3 Hz, 2 H).

3-[4-({2-[5-Chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}-ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]-propanoic Acid (136). Ester **135** (0.120 g, 0.143 mmol) was hydrolyzed according to the general procedure to afford **136** (0.101 g, 86% yield) as a white solid, mp 115–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53−2.75 (m, 4H), 2.78−2.85 (m, 2H), 2.87−2.95 (m, 2H), 3.03 (t, J = 6.6 Hz, 2H), 3.20−3.36 (m, 2 H), 3.98 (s, 2H), 6.12 (s, 1H), 6.40 (d, J = 8.8 Hz, 1H), 6.73 (dd, J = 7.4, 1.89 Hz, 1H), 6.76−6.85 (m, 3H), 6.94−7.08 (m, 5H), 7.28−7.37 (m, 6H), 7.38−7.44 (m, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.31 Hz, 2H). Anal. ($C_{41}H_{37}Cl_3N_2O_6S_2$) C, H, N. HRMS calcd for [$C_{41}H_{37}Cl_3N_2O_6S_2$ + H] 823.123 14; found 823.122 92.

Ethyl 3-[4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1*H*-indol-3-yl]ethyl}thio)phenyl]propanoate (128). 2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indole **26** (7.98 g, 18.4 mmol), ethyl 3-{4-[(2-oxoethyl)thio]phenyl}propanoate (15.03 g, 59.6 mmol), TFA (4.25 mL, 55.2 mmol), and Et_3SiH (35 mL, 219.1 mmol) were reacted following the general reductive alkylation procedure to yield, after purification via flash chromatography (20% EtOAc−hexanes), **128** (7.92 g, 64% yield) as a yellow oil.

Ethyl 3-[4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}thio)phenyl]propanoate (129). Indole **128** (7.61 g, 11.4 mmol), NaH (0.50 g, 12.5 mmol), Ph_2CHBr (5.1 g, 20.5 mmol) were reacted using the general N-alkylation conditions to afford, after purification via flash chromatography (16% EtOAc−hexanes), **129** (4.03 g, 42% yield) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9 H), 1.19−1.29 (m, 5 H), 2.59 (t, J = 7.9 Hz, 2 H), 2.87−2.95 (m, 3 H), 2.98−3.07 (m, 3 H), 3.65 (t, J = 7.4 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 6.36 (d, J = 8.8 Hz, 1 H), 6.69 (s, 1 H), 6.73 (dd, J = 8.8, 2.27 Hz, 1 H), 6.91 (d, J = 7.1 Hz, 3 H), 7.12 (d, J = 8.3 Hz, 2 H), 7.18−7.31 (m, 12 H), 7.32−7.43 (m, 4 H), 7.48−7.53 (m, 4 H).

Ethyl3-[4-({2-[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (130). NMO (2.23 g, 19.1 mmol) was added to a solution containing silyl ether **129** (3.9 g, 4.7 mmol), CH_3CN (0.1 M), and molecular sieves (1 g/mmol benzoate). After 10 min, TPAP (0.084 g, 0.24 mmol) was added and the mixture was heated to 40 °C. After 1.5 h the mixture was cooled and the filtrate was purified via flash chromatography (25% EtOAc−hexanes) to deliver **130** (3.51 g, 86% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9 H), 1.20−1.28 (m, 5 H), 2.64 (t, J = 7.7 Hz, 2 H), 2.96−3.06 (m, 4 H), 3.08−3.15 (m, 2 H), 3.20−3.27 (m, 2 H), 3.64 (t, J = 6.9 Hz, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 6.34 (d, J = 9.1 Hz, 1 H), 6.65 (s, 1 H), 6.72 (dd, J = 8.9, 2.1 Hz, 1 H), 6.87 (d, J = 7.3 Hz, 4 H), 7.03 (d, J = 2.0 Hz, 1 H), 7.15−7.25 (m, 10 H), 7.32−7.41 (m, 4 H), 7.45−7.51 (m, 4 H), 7.84 (d, J = 8.3 Hz, 2 H). HRMS calcd for [$C_{52}H_{54}ClNO_5SSi$ + H] 868.325 32; found 868.32521. Anal. ($C_{52}H_{54}ClNO_5SSi$) C, H, N.

Ethyl 3-[4-({2-[5-Chloro-1-(diphenylmethyl)-2-(2-hydroxyethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (131). TBAF (3.4 mL of a 1.0 M solution in THF, 3.4 mmol) was added to a solution of silyl ether **130** (2.45 g, 2.8 mmol) and THF (0.1 M) at 0 °C. The reaction mixture was allowed to warm to room temperature, and after 1 h it was quenched with aqueous NH_4Cl solution. Aqueous workup and flash chromatography (10% EtOAc−hexanes) afforded **131** (1.57 g, 89% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H), 2.66 (t, J = 7.7 Hz, 2 H), 2.97 (t, J = 6.5 Hz, 2 H), 3.05 (t, J = 7.6 Hz, 2 H), 3.12−3.19 (m, 2 H), 3.34−3.41 (m, 2 H), 3.59−3.66 (m, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.9, 2.1 Hz, 1 H), 6.92 (s, 1 H), 7.04 (dd, J = 6.7, 2.9 Hz, 4 H), 7.14 (d, J = 1.8 Hz, 1 H), 7.27−7.33 (m, 6 H), 7.43 (d, J = 8.3 Hz, 2 H), 7.86−7.92 (m, 2 H).

Ethyl 3-(4-{[2-(5-Chloro-1-(diphenylmethyl)-2-{2-[(methylsulfonyl)oxy]ethyl}-1*H*-indol-3-yl)ethyl]sulfonyl}phenyl)propanoate (132). MsCl (0.26 mL, 3.4 mmol) and Et_3N (0.58 mL, 4.2 mmol) were added to a solution of alcohol **131** (1.04 g, 1.65 mmol) in CH_2Cl_2 (0.02 M) at 0 °C. After 1 h the reaction mixture was warmed to room temperature. After 1 h, aqueous workup afforded **132** (1.21 g, 98% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 2.65 (t, J = 7.7 Hz, 2 H), 2.83 (s, 3 H), 3.05 (t, J = 7.7 Hz, 2 H), 3.16−3.25 (m, 4 H), 3.34−3.40 (m, 2 H), 4.03 (t, J = 6.9 Hz, 2 H), 4.13 (q, J = 7.1 Hz, 2 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.0 Hz, 1 H), 6.87 (s, 1 H), 7.02−7.09 (m, 4 H), 7.20 (d, J = 2.0 Hz, 1 H), 7.29−7.35 (m, 6 H), 7.42 (d, J = 8.6 Hz, 2 H), 7.90 (d, J = 8.3 Hz, 2 H).

Ethyl 3-[4-({2-[2-(2-Azidoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (133). A solution of mesylate **132** (1.17 g, 1.65 mmol), sodium azide (0.54 g, 8.3 mmol), and DMF (0.05 M) was heated to 60 °C. After 1 h the mixture was cooled and aqueous workup provided **132** (1.04 g, 96% yield) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3 H), 2.66 (t, J = 7.7 Hz, 2 H), 2.95 (t, J = 3.4 Hz, 2 H), 3.06 (t, J = 7.7 Hz, 2 H), 3.11−3.21 (m, 4 H), 3.33−3.40 (m, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 6.49 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 8.8, 2.01 Hz, 1 H), 6.87 (s, 1 H), 7.02−7.08 (m, 4 H), 7.13 (d, J = 2.0 Hz, 1 H), 7.28−7.34 (m, 6 H), 7.44 (d, J = 8.6 Hz, 2 H), 7.90 (d, J = 8.3 Hz, 2 H).

Ethyl 3-[4-({2-[2-(2-Aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (134). A suspension of azide **133** (1.0 g, 1.53 mmol), PPh_3 (0.66 g, 2.0 mmol, polymer supported loaded at 3mmol/g), and THF (0.1 M) was stirred overnight. H_2O (1 mL/mmol benzoate) was added, and the mixture was stirred overnight. The solution was concentrated and purified via flash chromatography (2% MeOH in CH_2Cl_2) to afford **134** (0.63 g, 65% yield) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3 H), 2.49−2.52 (m, 2 H), 2.55 (t, J = 7.1 Hz, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 2.76−2.83 (m, 2 H), 2.94−3.01 (m, 4 H), 3.52−3.60 (m, 2 H), 4.04 (q, J = 7.1 Hz, 2 H), 6.49 (d, J = 8.8 Hz, 2 H), 6.75 (dd, J = 8.8, 2.0 Hz, 1 H), 7.05−7.10 (m, 4 H), 7.12−7.17 (m, 2 H), 7.28−7.38 (m, 5 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.90 (d, J = 8.3 Hz, 2 H).

Ethyl 3-[4-({2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoate (137). To amine **134** (0.15 g, 0.24 mmol) was added (2-chlorophenyl)methanesulfonyl chloride (0.12 g, 0.53 mmol; see **114** preparation) using the Schotten−Baumann general procedure to generate the sulfonamide **137** (0.15 g, 76% yield) after purification by preparative TLC (2% MeOH in CH_2Cl_2 eluant).

3-[4-({2-[5-Chloro-2-(2-{[(2-chlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoic Acid (138). Ester **137** (0.15 g, 0.18 mmol) was hydrolyzed according to the general procedure to acid **138** (0.12 g, 83% yield) as a tan solid, mp 113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55−2.65 (m, 2 H), 2.66−2.75 (m, 2 H), 2.75−2.82 (m, 2 H), 2.84−2.94 (m, 2 H), 2.98−3.06 (m, 2 H), 3.20−3.32 (m, 2 H), 4.33 (s, 2 H), 5.98−6.08 (t, J = 5.9 Hz, 1H), 6.38 (d, J = 9.06 Hz, 1 H), 6.76 (s, 1 H), 6.78 (d, J = 2.01 Hz, 1 H), 6.96−7.06 (m, 4 H), 7.12−7.37 (m, 10 H), 7.38−7.41 (m, 1 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.89 (d, J = 8.3 Hz, 2 H). HRMS calcd for [$C_{41}H_{38}Cl_2N_2O_6S_2$ + H] 789.162 11; found 789.163 11.

Methyl 3-[4-({2-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]-amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)-phenyl]propanoate (139). To amine **43** (0.085 g, 0.14 mmol) was added (2,6-difluorophenyl)methanesulfonyl chloride **78** (0.038 g, 0.17 mmol) using the Schotten−Baumann general procedure to afford the sulfonamide **139** (0.047 g, 42% yield).

3-[4-({2-[5-Chloro-2-(2-{[(2,6-difluorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]ethyl}sulfonyl)phenyl]propanoic Acid (140). Ester **139** (0.046 g, 0.058 mmol) was hydrolyzed according to the general procedure to afford acid **140** (38 mg, 83% yield) as a yellow solid, mp 132–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56−2.68 (m, 2 H), 2.73−2.81 (m, 4 H), 2.82−2.95 (m, 2 H), 2.97−3.13 (m, 2 H), 3.18−3.38 (m, 2 H), 4.22 (s, 2 H), 6.18 (br s, 1 H), 6.39 (d, J = 8.8 Hz, 1 H), 6.70−6.83 (m, 3 H), 6.83−6.95 (m, 2 H), 6.98−7.09 (m, 4 H), 7.27−7.36 (m, 6 H),

7.41−7.43 (m, 1 H), 7.43−7.47 (m, J = 8.3 Hz, 2H), 7.80−7.97 (m, 2 H). HRMS calcd for $[C_{41}H_{37}ClF_2N_2O_6S_2 + H]$ 791.182 24; found 791.182 57.

Biological Procedures. All in vivo experiments were performed in accordance with protocols approved by Wyeth's Institutional Animal Care and Use Committee. GLU micelle, MC-9, and rat whole blood assays were previously described,[41] as were isothermal calorimetry, human whole blood assay, and COX assays.[44]

A549 COX-2 Cell Assay. A-549 cells were plated at 0.2 million cells/well in 1 mL of F12K medium containing 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 100 units/mL penicillin, 100 μg/mL streptomycin, and 10% FBS. After 16–24 h, the cells were washed with PBS three times and 1 mL of medium containing 2% FBS and 1 ng/mL IL-1β was added. The negative controls did not contain IL-1β, and inhibitor was added to the appropriate wells. The next day, the supernatant was collected from all wells.

The cells were then washed with medium containing 2% FBS, IL-1β, and inhibitor where appropriate. The cells were then incubated for 15 min with medium containing 2% FBS, IL-1β, inhibitor, and arachidonic acid (1 μM) where appropriate. After 15 min at 37 °C, the supernatant was collected, centrifuged, transferred to a fresh plate, and stored at –20 °C until PGE_2 production was analyzed by ELISA. By measuring the PGE_2 production that occurs in the 15 min of incubation after overnight induction of COX-2, we were able to determine the effect of bypassing $cPLA_2\alpha$ with exogenous arachidonic acid.

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 DMSO/PEG-400 (50/50) via tail vein injection. For oral administration, rats (n = 3) were dosed via gavage at 25 mg/kg. Compounds were made at 37.5 mg/mL in Phosal vehicle (50% Phosal 53 MCT, 5% Tween-80, 15% Labrasol and is q.s. to 100% with propylene carbonate), diluted to 6.25 mg/mL with H_2O, and then 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).

Carrageenan Air Pouch. 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 appropriate dose of **2**, **111**, **121**, or Phosal vehicle (50% Phosal 53 MCT, 5% Tween-80, 15% Labrasol and is q.s. to 100% with propylene carbonate) was administered to the rats by oral gavage. Compound at 37.5 mg/mL in Phosal vehicle was diluted with the appropriate amount of water and administered at 4 mL/kg. 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 3407.35g for 10 min, and 300 μL of each supernatant was precipitated with 800 μL of ice-cold methanol. The samples were well vortexed and were kept at –80 °C overnight. Before performance of the PGE_2 test, the samples were centrifuged again. Supernatants were used directly by a dilution of 1:5 or greater in assay buffer (supplied in the PGE_2 kit) to locate the PGE_2 production within the linear range of the PGE_2 standard curve (PGE_2 ELISA kit, Assay Design Inc. (Ann Arbor, MI)). Generally, the concentration of the linear range was from 62.5 to 1000 pg/mL. 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} values were extrapolated from the dose response curve for each compound. There were six to eight mice per group.

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 carrageenan-induced rat paw edema model was adapted from procedures previously described.[78,79] The volume of the left hind footpad of the rat was measured using an Ugo Basile plethysmometer prior to dosing. Compounds **2**, **111**, and **121** were dissolved at 37.5 mg/mL in Phosal vehicle. Compound was diluted with the appropriate amount of water and administered at 4 mL/kg. 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. There were 10 animals per group. Inhibition was calculated using the following formula:

$$\text{percent inhibtion} = \{1 - [(\text{3 h paw volume}) - (\text{0 h paw volume (test group)}]/[(\text{3 h paw volume}) - (\text{0 h paw volume (vehicle group)}]\} \times 100$$

The maximum inhibition effect observed is ~50% when dosed with naproxen po at a dose of ≥10 mg/kg, and the ED_{50} is defined as the dose of the $cPLA_2\alpha$ inhibitor that inhibits 25% of edmea, or half-the maximal value.

Collagen Induced Arthritis (CIA) Model. Arthritis was induced by immunization with bovine type II collagen (Chondrex, Redmond, WA) that had been dissolved in 0.1 M acetic acid to a concentration of 2 mg/mL. This solution was then emulsified 1:1 with either complete Freund's Adjuvant (Sigma Chemical Co., St. Louis, MO) or incomplete Freund's Adjuvant (Sigma Chemical Co., St. Louis, MO).

An appropriate amount **2**, **111**, or **121** was weighed to make a stock solution of 37.5 mg/mL Phosal vehicle. For each treatment day over the course of 31 days the stock solution was diluted daily with deionized water to a final concentration of 10 mg/mL **111** and dosed at 100 mg/kg (10 mL/kg) and the compounds were dosed b.i.d. via oral gavage.

The mice were monitored daily for signs of arthritis using the scoring system shown below. When 10% of the mice demonstrated signs of arthritis, all the mice were randomly assigned to treatment groups. On the day that the animals were assigned to a treatment group, the mice began receiving daily doses via oral gavage of compound or the vehicle control. The oral dose administration was conducted for 31 days; one assigned group in the oral study was left untreated. The disease severity was scored in a blinded fashion: no arthritis (score 0); one or two swollen digits (score 1); three or more swollen digits or mild to moderate swelling of the entire paw (score 2); extensive swelling of the entire paw (score 3); resolution of swelling with ankylosis of the paw (score 4). All paws were evaluated for each animal; therefore, the maximum score per animal was 16.

Following euthanasia with CO_2 on day 32 after 31 days of treatment, all four paws of nine animals from each of the three groups were placed in 10% neutral buffered formalin, decalcified, processed, paraffin-embedded, and prepared as standard hematoxylin and eosin-stained glass slides. All slides were evaluated in a blinded fashion by a board certified veterinary pathologist using the following qualitative scoring system for arthritis severity: "grade 0" for no abnormal findings (normal synovial membrane at 1–3 synoviocytes thick, absence of inflammatory cells, and smooth articulating cartilage surfaces); "grade 1" (synoviocyte hypertrophy, slight synovial membrane fibrosis, slight to mild inflammatory cell infiltrates into the synovial membrane/articular capsule and/or joint space); "grade 2" (grade 1 plus mild to moderate inflammatory cell infiltrates, pannus formation (if present) is minimal with superficial cartilage erosion); "grade 3" (grade 2 plus marked inflammatory cell infiltrates and fibrosis, mild to severe erosion of the cartilage extending into subchondral bone); and "grade 4" (loss of joint integrity through erosion or destruction with bone remodeling, massive inflammatory cell infiltrates, fibrosis, and ankylosis).

Adjuvant Induced Arthritis (AIA) Model. Rats were injected intradermally with 0.1 mL of Freund's adjuvant-complete at the

tail. Each milliliter contained 1 mg of *Mycobacterium tuberculosis* heat-killed and dried, 0.85 mL of mineral oil, and 0.15 mL of mannide monooleate. After 8 days the animals were randomized into five groups, each group containing six rats. The eight groups were dosed orally using Phosal vehicle as described above. The animals were treated for 11 days. During the 11 treatment days, the severity of arthritis was monitored daily. This was done using a 0–3 scale for swelling and for erythema of the hindpaws (0 = normal paw, 1 = mild, 2 = moderate, 3 = severe). The maximum possible score per day was 12.

At the end of the study, treatment day 11, the rats were euthanized with CO_2. During necropsy, the tarsal joints were removed and fixed in 10% buffered formalin. After decalcification, histologic sections were obtained and stained with hematoxylin and eosin or safranin O–fast green stain. Subsequently, an examiner blinded to the treatment groups evaluated the slides. Synovial tissue from tarsal joints was evaluated on the basis of synovial hyperplasia (score 0–3), fibroplasia (score 0–3), inflammatory cell infiltration (score 0–3), and pannus formation (score 0–2). Articular cartilage was evaluated using Mankin's histological grading system,[64] based on structure (score 0–6), cellularity (score 0–3), safranin-O staining (score 0–4), and tidemark integrity (score 0–1).

Allergen Induced Sheep Bronchoconstriction Model. Allergic sheep weighing 27−50 kg were used to assess efficacy of test articles. All sheep had previously been shown to develop both early and late bronchial responses to inhaled Ascaris Suum antigen. The sheep were conscious and were restrained in a modified shopping cart in the prone position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine a balloon catheter was advanced through one nostril into the lower esophagus. The animals were intubated with a cuffed endotracheal tube through the other nostril with a flexible fiberoptic bronchoscope as a guide. Animals were challenged via the airways with Ascaris Suum antigen (Greer Diagnostics, Lenoir, NC), and breath-by-breath determination of mean pulmonary resistance (R_L) was measured with the esophageal balloon technique as described previously.[80] To assess bronchial responsiveness (AHR), the day following allergen challenge cumulative concentration–response curves to carbachol were generated by measuring specific lung resistance immediately after inhalation of buffer and after each consecutive administration of 10 breaths of increasing concentrations of carbachol. The provocation test was discontinued when specific lung resistance increased by more than 400% from the postsaline value or after the highest carbachol concentration had been administered.

To determine efficacy by oral administration, test articles were administered at 10 mg/kg b.i.d. on the day prior to antigen challenge and again 2 h prior to challenge and 8 h after challenge. For oral administration at 10 mg/kg, test articles were dissolved in Phosal (150 mg/mL stock solution in 50% Phosal 53 MCT, 5% Tween-80, 15% Labrasol and is q.s. to 100% with propylene carbonate). On the day of the experiment the stock solution was diluted to 40 mg/mL with water and dosed at 0.25 mL/kg. In each experiment both the early and late phase asthmatic response and AHR were measured as described above. There were two to three sheep in each test group. Changes in airway resistance after administration of test aricles were compared to historical control values for each individual sheep.

Acknowledgment. The authors thank Molly Hoke, Wei Li, Jianchang Li, and Dianne DeVincentis for the preparation of chemical intermediates; Yelena Leathurby for help with the AIA study; Nelson Huang, Ying Ge, Walter Massefski, Ning Pan, and Peter Tate for analytical support; Wen Zhang, Weili Duan, and Yajuan Zhao for assay support; Nevana Mollova, Uma Ruat, and Elizabeth Vayntrub for providing analytical analysis of drug concentrations; and Douglas Shorten and Shannon Chesley for coordinating animal PK studies. We also thank Howard Sard, Anu Mahadevan, Mario Gonzalez, Vishnu Hegede, and Shanghao Liu of Organix, Inc. for the preparation of chemical intermediates.

Supporting Information Available: Purity data from HPLC analysis or full combustion data for all final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added in Proof. Human $cPLA_2\zeta$ (PLA2gIVf) was expressed in COS-M6 cells and the cleared lysate was assayed analogously to the $cPLA_2\beta$ assay. The maximum inhibition observed for **121** was 30% at 2 μM. In contrast, $cPLA_2\alpha$ assayed in parallel was 90% inhibited at 30 nM and had an IC50 = 8 nM.

References

(1) Ramesha, C. S.; Pickett, W. C. Platelet-activating factor and leukotriene biosynthesis is inhibited in polymorphonuclear leukocytes depleted of arachidonic acid. *J. Biol. Chem.* **1986**, *261* (17), 7592–7595.
(2) Suga, K.; Kawasaki, T.; Blank, M. L.; Snyder, F. An arachidonoyl (polyenoic)-specific phospholipase A_2 activity regulates the synthesis of platelet-activating factor in granulocytic HL-60 cells. *J. Biol. Chem.* **1990**, *265* (21), 12363–12371.
(3) Uozumi, N.; Kume, K.; Nagase, T.; Nakatani, N.; Ishii, S.; Tashiro, F.; Komagata, Y.; Maki, K.; Ikuta, K.; Ouchi, Y.; Miyazaki, J.-i.; Shimizu, T. Role of cytosolic phospholipase A_2 in allergic response and parturition. *Nature* **1997**, *390* (6660), 618–622.
(4) FitzGerald, G. A.; Patrono, C. The coxibs, selective inhibitors of cyclooxygenase-2. *New Engl. J. Med.* **2001**, *345* (6), 433–442.
(5) Funk, C. D. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* **2001**, *294* (5548), 1871–1875.
(6) Singh, V. P.; Patil, C. S.; Kulkarni, S. K. Differential effect of zileuton, a 5-lipoxygenase inhibitor, against nociceptive paradigms in mice and rats. *Pharmacol., Biochem. Behav.* **2005**, *81*, 433–439.
(7) Honda, Z. I., S.; Shimizu, T. *J. Biochem. (Tokyo)* **2002**, *131* (6), 773–779.
(8) Tsuda, M. I. S.; Masuda, T.; Hasegawa, S.; Nakamura, K.; Nagata, K.; Yamashita, T.; Furue, H.; Tozaki-Saitoh, H.; Yoshimura, M.; Koizumi, S.; Shimizu, T.; Inoue, K. Reduced pain behaviors and extracellular signal-related protein kinase activation in primary sensory neurons by peripheral tissue injury in mice lacking platelet-activating factor receptor. *J. Neurochem.* **2007**, *102* (5), 1658–1668.
(9) Bonventre, J. V.; Sapirstein, A. Group IV cytosolic phospholipase A_2 (PLA_2) function: insights from the knockout mouse. *Adv. Exp. Med. Biol.* **2002**, 507. *Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury*; Marnett, L. J., Nigam, S., Honn, K. V., Eds.; Kluwer Academic/Plenum Publishers: New York, 2002; Vol. 5, pp 25–31.
(10) Uozumi, N.; Shimizu, T. Roles for cytosolic phospholipase $A_2\alpha$ as revealed by gene-targeted mice. *Prostaglandins Other Lipid Mediators* **2002**, *68–69*, 59–69.
(11) Sapirstein, A.; Bonventre, J. V. Specific physiological roles of cytosolic phospholipase A_2 as defined by gene knockouts. *Biochim. Biophys. Acta* **2000**, *1488* (1–2), 139–148.
(12) Hegen, M.; Sun, L.; Uozumi, N.; Kume, K.; Goad, M. E.; Nickerson-Nutter, C. L.; Shimizu, T.; Clark, J. D. Cytosolic phospholipase $A_2\alpha$-deficient mice are resistant to collagen-induced arthritis. *J. Exp. Med.* **2003**, *197* (10), 1297–1302.
(13) Nagase, T.; Uozumi, N.; Ishii, S.; Kume, K.; Izumi, T.; Ouchi, Y.; Shimizu, T. Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A_2. *Nat. Immunol.* **2000**, *1* (1), 42–46.
(14) Bonventre, J. V.; Huang, Z.; Taheri, M. R.; O'Leary, E.; Li, E.; Moskowitz, M. A.; Sapirstein, A. Reduced fertility and postischemic brain injury in mice deficient in cytosolic phospholipase A_2. *Nature* **1997**, *390* (6660), 622–625.
(15) Klivenyi, P.; Beal, M. F.; Ferrante, R. J.; Andreassen, O. A.; Wermer, M.; Chin, M.-R.; Bonventre, J. V. Mice deficient in group IV cytosolic phospholipase A_2 are resistant to MPTP neurotoxicity. *J. Neurochem.* **1998**, *71* (6), 2634–2637.
(16) Hong, K. H.; Bonventre, J. C.; O'Leary, E.; Bonventre, J. V.; Lander, E. S. Deletion of cytosolic phospholipase A_2 suppresses ApcMin-induced tumorigenesis. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98* (7), 3935–3939.
(17) Takaku, K.; Sonoshita, M.; Sasaki, N.; Uozumi, N.; Doi, Y.; Shimizu, T.; Taketo, M. M. Suppression of intestinal polyposis in ApcD716 knockout mice by an additional mutation in the cytosolic phospholipase A_2 gene. *J. Biol. Chem.* **2000**, *275* (44), 34013–34016.
(18) Marusic, S.; Leach, M. W.; Pelker, J. W.; Azoitei, M. L.; Uozumi, N.; Cui, J.; Shen, M. W. H.; DeClercq, C. M.; Miyashiro, J. S.; Carito, B. A.; Thakker, P.; Simmons, D. L.; Leonard, J. P.; Shimizu, T.; Clark, J. D. Cytosolic phospholipase $A_2\alpha$-deficient mice are resistant to experimental autoimmune encephalomyelitis. *J. Exp. Med.* **2005**, *202* (6), 841–851.

(19) Banville, J.; Gai, Y.; Plamondon, S.; Remillard, R.; Martel, A.; Bouthillier, G.; Johnson, G.; Brassil, P.; Gregor, K.; Burke, J.; Balasubramanian, B. Preparation and Evaluation of BMS-229724 Analogues as Inhibitors of Cytosolic Phospholipase A_2. *Abstracts of Papers*, 223rd National Meeting of the American Chemical Society, Orlando, FL, April 7–11, 2002; American Chemical Society: Washington, DC, 2002; MEDI-055.

(20) Lio, Y.-C.; Reynolds, L. J.; Balsinde, J.; Dennis, E. A. Irreversible inhibition of Ca^{2+}-independent phospholipase A_2 by methyl arachidonyl fluorophosphonate. *Biochim. Biophys. Acta* **1996**, *1302* (1), 55–60.

(21) Conde-Frieboes, K.; Reynolds, L. J.; Lio, Y.-C.; Hale, M. R.; Wasserman, H. H.; Dennis, E. A. Activated ketones as inhibitors of intracellular Ca^{2+}-dependent and Ca2+-independent phospholipase A_2. *J. Am. Chem. Soc.* **1996**, *118* (24), 5519–5525.

(22) Burke, J. R.; Davern, L. B.; Stanley, P. L.; Gregor, K. R.; Banville, J.; Remillard, R.; Russell, J. W.; Brassil, P. J.; Witmer, M. R.; Johnson, G.; Tredup, J. A.; Tramposch, K. M. BMS-229724 is a tight-binding inhibitor of cytosolic phospholipase A_2 that acts at the lipid/water interface and possesses anti-inflammatory activity in skin inflammation models. *J. Pharmacol. Exp. Ther.* **2001**, *298* (1), 376–385.

(23) Burke, J. R.; Gregor, K. R.; Padmanabha, R.; Banville, J.; Witmer, M. R.; Davern, L. B.; Manly, S. P.; Tramposch, K. M. A β-lactam inhibitor of cytosolic phospholipase A_2 which acts in a competitive, reversible manner at the lipid/water interface. *J. Enzyme Inhib.* **1998**, *13* (3), 195–206.

(24) Street, I. P.; Lin, H.-K.; Laliberté, F.; Ghomashchi, F.; Wang, Z.; Perrier, H.; Tremblay, N. M.; Huang, Z.; Weech, P. K.; Gelb, M. H. Slow- and tight-binding inhibitors of the 85-kDa human phospholipase A_2. *Biochemistry.* **1993**, *32* (23), 5935–5940.

(25) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. The conformations of halichlorine and the pinnaic acids: nitrogen inversion as a possible determinant of biological profile. *Helv. Chim. Acta* **2000**, *83* (9), 2344–2351.

(26) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. Pinnaic acid and tauropinnaic acid: two novel fatty acids composing a 6-azaspiro[4.5]decane unit from the Okinawan bivalve *Pinna muricata*. *Tetrahedron Lett.* **1996**, *37* (22), 3871–3874.

(27) Lucas, R.; Ubeda, A.; Paya, M.; Alves, M.; Del Olmo, E.; Lopez, J. L.; San Feliciano, A. Synthesis and enzyme inhibitory activities of a series of lipidic diamine and aminoalcohol derivatives on cytosolic and secretory phospholipases A_2. *Bioorg. Med. Chem. Lett.* **2000**, *10* (3), 285–288.

(28) Varghese, J.; Rydel, R. E.; Dappen, M. S.; Thorsett, E. D. Preparation of 4-Benzyl-2-phenylpyrimidines as Phospholipase A_2 Inhibitors. 99-US26550 2000027824, 19991110, 2000.

(29) Lehr, M. Structure−activity relationship studies on (4-acylpyrrol-2-yl)alkanoic acids as inhibitors of the cytosolic phospholipase A_2: variation of the alkanoic acid substituent, the acyl chain and the position of the pyrrole nitrogen. *Eur. J. Med. Chem.* **1997**, *32* (10), 805–814.

(30) Lehr, M. Structure−activity relationships of (4-acylpyrrol-2-yl)alkanoic acids as inhibitors of the cytosolic phospholipase A_2: variation of the substituents in positions 1, 3, and 5. *J. Med. Chem.* **1997**, *40* (21), 3381–3392.

(31) Lehr, M. 3-(Octadecanoylaminomethyl)indole-2-carboxylic acid derivatives and 1-methyl-3-octadecanoylindole-2-carboxylic acid as inhibitors of cytosolic phospholipase A_2. *Arch. Pharm.* **1996**, *329* (8–9), 386–392.

(32) Seno, K.; Okuno, T.; Nishi, K.; Murakami, Y.; Watanabe, F.; Matsuura, T.; Wada, M.; Fujii, Y.; Yamada, M.; Ogawa, T.; Okada, T.; Hashizume, H.; Kii, M.; Hara, S.-i.; Hagishita, S.; Nakamoto, S.; Yamada, K.; Chikazawa, Y.; Ueno, M.; Teshirogi, I.; Ono, T.; Ohtani, M. Pyrrolidine inhibitors of human cytosolic phospholipase A_2. *J. Med. Chem.* **2000**, *43* (6), 1041–1044.

(33) Seno, K.; Okuno, T.; Nishi, K.; Murakami, Y.; Yamada, K.; Nakamoto, S.; Ono, T. Pyrrolidine inhibitors of human cytosolic phospholipase A_2. Part 2. Synthesis of potent and crystallized 4-triphenylmethylthio derivative "pyrrophenone". *Bioorg. Med. Chem. Lett.* **2001**, *11* (4), 587–590.

(34) Ono, T.; Yamada, K.; Chikazawa, Y.; Ueno, M.; Nakamoto, S.; Okuno, T.; Seno, K. Characterization of a novel inhibitor of cytosolic phospholipase $A_2\alpha$, pyrrophenone. *Biochem. J.* **2002**, *363* (3), 727–735.

(35) Connolly, S.; Bennion, C.; Botterell, S.; Croshaw, P. J.; Hallam, C.; Hardy, K.; Hartopp, P.; Jackson, C. G.; King, S. J.; Lawrence, L.; Mete, A.; Murray, D.; Robinson, D. H.; Smith, G. M.; Stein, L.; Walters, I.; Wells, E.; Withnall, W. J. Design and synthesis of a novel and potent series of inhibitors of cytosolic phospholipase A_2 based on a 1,3-disubstituted propan-2-one skeleton. *J. Med. Chem.* **2002**, *45* (6), 1348–1362.

(36) Kokotos, G.; Kotsovolou, S.; Six, D. A.; Constantinou-Kokotou, V.; Beltzner, C. C.; Dennis, E. A. Novel 2-oxoamide inhibitors of human group IVA phospholipase A2. *J. Med. Chem.* **2002**, *45* (14), 2891–2893.

(37) Kokotos, G.; Six, D. A.; Loukas, V.; Smith, T.; Constantinou-Kokotou, V.; Hadjipavlou-Litina, D.; Kotsovolou, S.; Chiou, A.; Beltzner, C. C.; Dennis, E. A. Inhibition of group IVA cytosolic phospholipase A_2 by novel 2-oxoamides in vitro, in cells, and in vivo. *J. Med. Chem.* **2004**, *47* (14), 3615–3628.

(38) Lehr, M. Inhibitors of cytosolic phospholipase $A_2\alpha$ as potential anti-inflammatory drugs. *Anti-Inflammatory Anti-Allergy Agents Med. Chem.* **2006**, *5* (2), 149–161.

(39) Magrioti, V.; Kokotos, G. Synthetic inhibitors of group IVA and group VIA phospholipase A_2. *Anti-Inflammatory Anti-Allergy Agents Medicinal Chemistry* **2006**, *5* (2), 189–203.

(40) Clark, J. D.; Tam, S. Potential therapeutic uses of phospholipase A_2 inhibitors. *Expert Opin. Ther. Pat.* **2004**, *14* (7), 937–950.

(41) McKew, J. C.; Foley, M. A.; Thakker, P.; Behnke, M. L.; Lovering, F. E.; Sum, F.-W.; Tam, S.; Wu, K.; Shen, M. W. H.; Zhang, W.; Gonzalez, M.; Liu, S.; Mahadevan, A.; Sard, H.; Khor, S. P.; Clark, J. D. Inhibition of cytosolic phospholipase $A_2\alpha$: hit to lead optimization. *J. Med. Chem.* **2006**, *49* (1), 135–158.

(42) Fries, S.; Grosser, T.; Price, T. S.; Lawson, J. A.; Kapoor, S.; Demarco, S.; Pletcher, M. T.; Wiltshire, T.; Fitzgerald, G. A. Marked interindividual variability in the response to selective inhibitors of cyclooxygenase-2. *Gastroenterology* **2006**, *130* (1), 55–64.

(43) Brooks, C. D. W.; Summers, J. B. Modulators of leukotriene biosynthesis and receptor activation. *J. Med. Chem.* **1996**, *39* (14), 2629–2654.

(44) Lee, K. L.; Foley, M. A.; Chen, L.; Behnke, M. L.; Lovering, F. E.; Kirincich, S. J.; Wang, W.; Shim, J.; Tam, S.; Shen, M. W. H.; Khor, S.; Xu, X.; Goodwin, D. G.; Ramarao, M. K.; Nickerson-Nutter, C.; Donahue, F.; Ku, M. S.; Clark, J. D.; McKew, J. C. Discovery of ecopladib, an indole inhibitor of cytosolic phospholipase $A_2\alpha$. *J. Med. Chem.* **2007**, *50* (6), 1380–1400.

(45) McKew, J. C.; Lovering, F.; Clark, J. D.; Bemis, J.; Xiang, Y.; Shen, M.; Zhang, W.; Alvarez, J. C.; Joseph-McCarthy, D. Structure−activity relationships of indole cytosolic phospholipase $A_2\alpha$ inhibitors: substrate mimetics. *Bioorg. Med. Chem. Lett.* **2003**, *13* (24), 4501–4504.

(46) Yaksh, T. L.; Kokotos, G.; Svensson, C. I.; Stephens, D.; Kokotos, C. G.; Fitzsimmons, B.; Hadjipavlou-Litina, D.; Hua, X.-Y.; Dennis, E. A. Systemic and intrathecal effects of a novel series of phospholipase A_2 inhibitors on hyperalgesia and spinal prostaglandin E_2 release. *J. Pharmacol. Exp. Ther.* **2006**, *316* (1), 466–475.

(47) Six, D. A.; Barbayianni, E.; Loukas, V.; Constantinou-Kokotou, V.; Hadjipavlou-Litina, D.; Stephens, D.; Wong, A. C.; Magrioti, V.; Moutevelis-Minakakis, P.; Baker, S. F.; Dennis, E. A.; Kokotos, G. Structure−activity relationship of 2-oxoamide inhibition of group IVA cytosolic phospholipase A_2 and group V secreted phospholipase A_2. *J. Med. Chem.* **2007**, *50* (17), 4222–4235.

(48) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. A general method for C3 reductive alkylation of indoles. *Tetrahedron Lett.* **2003**, *44* (24), 4589–4591.

(49) Appleton, J. E.; Dack, K. N.; Green, A. D.; Steele, J. A mild and selective C-3 reductive alkylation of indoles. *Tetrahedron Lett.* **1993**, *34* (9), 1529–1532.

(50) Balabyshevich, A. G.; Yares'ko, N. S.; Suvorov, N. N. Preparation of 5-chloro- and 5-methyl-2-(2-aminoethyl)indoles. *Zh. Vses. Khim. Ova. im. D. I. Mendeleeva* **1975**, *20* (2), 239–240.

(51) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992, p 499.

(52) Nakayama, J.; Tanuma, M.; Honda, Y.; Hoshino, M. Reaction of arylmethanesulfonyl and styrylmethanesulfonyl chlorides with triethylamine. *Tetrahedron Lett.* **1984**, *25* (40), 4553–4556.

(53) Ramarao, M. K. Manuscript in preparation.

(54) Ohto, T.; Uozumi, N.; Hirabayashi, T.; Shimizu, T. Identification of novel cytosolic phospholipase A_2s, murine cPLA$_2$d, e, and z, which form a gene cluster with cPLA$_2\beta$. *J. Biol. Chem.* **2005**, *280* (26), 24576–24583.

(55) Abraham, W. M.; Ahmed, A.; Cortes, A.; Sielczak, M. W.; Hinz, W.; Bouska, J.; Lanni, C.; Bell, R. L. The 5-lipoxygenase inhibitor zileuton blocks antigen-induced late airway responses, inflammation and airway hyperresponsiveness in allergic sheep. *Eur. J. Pharmacol.* **1992**, *217* (2–3), 119–126.

(56) Bell, R. L. The development of zileuton (ZYFLO) and the *N*-hydroxyurea class of 5-lipoxygenase inhibitors. *Novel Inhibitors Leukotrienes* **1999**, 235–249.

(57) Smith, C. J.; Zhang, Y.; Koboldt, C. M.; Muhammad, J.; Zweifel, B. S.; Shaffer, A.; Talley, J. J.; Masferrer, J. L.; Seibert, K.; Isakson, P. C. Pharmacological analysis of cyclooxygenase-1 in inflammation. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95* (22), 13313–13318.

(58) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.;

Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). *J. Med. Chem.* **1997**, *40* (9), 1347–1365.

(59) Thoren, S.; Jakobsson, P.-J. Coordinate up- and down-regulation of glutathione-dependent prostaglandin E synthase and cyclooxygenase-2 in A549 cells. Inhibition by NS-398 and leukotriene C4. *Eur. J. Biochem.* **2000**, *267* (21), 6428–6434.

(60) Masferrer, J. L.; Zweifel, B. S.; Manning, P. T.; Hauser, S. D.; Leahy, K. M.; Smith, W. G.; Isakson, P. C.; Seibert, K. Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91* (8), 3228–3232.

(61) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. 4-[5-Methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. *J. Med. Chem.* **2000**, *43* (5), 775–777.

(62) Otterness, I. G.; Bliven, M. L. *Laboratory Models for Testing Nonsteroidal Antiinflammatory Drugs*; John Wiley & Sons: New York, 1985; pp 111–251.

(63) Mukherjee, A.; Hale, V. G.; Borga, O.; Stein, R. Predictability of the clinical potency of NSAIDs from the preclinical pharmacodynamics in rats. *Inflammation Res.* **1996**, *45* (11), 531–540.

(64) Mankin, H. J.; Dorfman, H. L. L. Z. A. Biochemical and metabolic abnormalities in articular cartilage from osteoarthritic human hip. *J. Bone Jt. Surg., Am. Vol.* **1971**, *53*, 523–537.

(65) Abraham, W. M.; Perruchoud, A. P. Role of arachidonic acid metabolites in allergen-induced late responses. *Respir.: Int. Rev. Thorac. Dis.* **1989**, *56* (1–2), 48–56.

(66) Jones, T. R.; Labelle, M.; Belley, M.; Champion, E.; Charette, L.; Evans, J.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Lord, A.; et al. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D_4 receptor antagonist. *Can. J. Physiol. Pharmacol.* **1995**, *73* (2), 191–201.

(67) Jones, T. R.; Labelle, M.; Belley, M.; Champion, E.; Charette, L.; Evans, J.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Lord, A.; et al. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D_4 receptor antagonist. *Can. J. Physiol. Pharmacol.* **1995**, *73* (6), 747. [Erratum to document cited in CA122: 281908]

(68) Abraham, W. M.; Stevenson, J. S.; Garrido, R. A possible role for PAF in allergen-induced late responses: modification by a selective antagonist. *J. Appl. Physiol.* **1989**, *66* (5), 2351–2357.

(69) Tomioka, K.; Garrido, R.; Ahmed, A.; Stevenson, J. S.; Abraham, W. M. YM461, a PAF antagonist, blocks antigen-induced late airway responses and airway hyperresponsiveness in allergic sheep. *Eur. J. Pharmacol.* **1989**, *170* (3), 209–215.

(70) Abad-Zapatero, C.; Metz James, T. Ligand efficiency indices as guideposts for drug discovery. *Drug Discovery Today* **2005**, *10* (7), 464–469.

(71) Kuntz, I. D.; Chen, K.; Sharp, K. A.; Kollman, P. A. The maximal affinity of ligands. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96* (18), 9997–10002.

(72) Six et al[47] have recently reported on the SAR of 2-oxoamide inhibitors of $cPLA_2\alpha$. These compounds were potent with Xi_{50} values as low as 5×10^{-3} where Xi_{50} is the concentration of the inhibitor at which 50% inhibition is detected with units of mole fraction calculated by taking the number of moles of inhibitor divided by the total number of moles of substrate plus inhibitor plus detergent. In this paper, the corresponding Xi_{50} for efipladib (**111**) and WAY-196025 (**121**) are 3.4×10^{-5} and 8.7×10^{-6}, respectively, or 147- to 575-fold more potent than the 2-oxoamides. Some of this difference may be due to differences in the assay. Although we have not synthesized and tested the most active compound by Six et al., we have made AX006 of their most recent paper[46] and the Shionogi pyrrephenone. In our GLU micelle assay, the Xi_{50} values for AX006 and the pyrrephenone are 4×10^{-3} and 1×10^{-4}, respectively. This is 4- to 5-fold lower than the values reported in the Six assay, suggesting that **111** and **121** may be only 30- to 10- fold more potent in vitro. Somewhat surprisingly given the activity against $cPLA_2\alpha$, the best 2-oxoamide (**17b**) is extraordinarily potent in the rat carrageenan paw edema model with $ED_{50} = 20\mu g/kg$, which is 200-fold more potent than indomethacin. This finding was even more surprising, given that the almost identical compound (compound **38** (4*S*)-4-(2-oxohexadecanamido)octanoic acid) (Xi_{50} = 0.008 mM), which is essentially equipotent against $cPLA_2\alpha$as **17b** (5*S*)-5-(2-oxohexadecanamido)nonanoic acid (Xi_{50} = 0.005 mM), is 160-fold less active in the CPE assay. We would not anticipate a significantly different metabolic profile for these molecules given that the carboxylate and oxoamides are the only functional groups and are separated by either four or five methylenes. Thus, in the absence of PK data, cellular assays, and whole blood assay data, we would question if the in vivo activity was consistent with the in vitro activity.

(73) Bhat, G. A.; Siddappa, S. Synthesis of indole 2-carboxaldehydes, 2-(2-aminoethyl) and 2-(2-aminopropyl) indoles. *J. Indian Chem. Soc.* **1974**, *51* (3), 427–432.

(74) Folkes, A.; Roe, M. B.; Sohal, S.; Golec, J.; Faint, R.; Brooks, T.; Charlton, P. Synthesis and in vitro evaluation of a series of diketopiperazine inhibitors of plasminogen activator inhibitor-1. *Bioorg. Med. Chem. Lett.* **2001**, *11* (19), 2589–2592.

(75) Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. Palladium catalyzed cross-coupling reaction of functionalized alkyltrifluorosilanes with aryl halides. *Tetrahedron Lett.* **1994**, *35* (35), 6507–6510.

(76) Hamann, P. R.; Hinman, L. M.; Hollander, I.; Beyer, C. F.; Lindh, D.; Holcomb, R.; Hallett, W.; Tsou, H.-R.; Upeslacis, J.; Shochat, D.; Mountain, A.; Flowers, D. A.; Bernstein, I. Gemtuzumab ozogamicin, a potent and selective anti-CD33 antibody−calicheamicin conjugate for treatment of acute myeloid leukemia. *Bioconjugate Chem.* **2002**, *13* (1), 47–58.

(77) Taylor, E. C.; Liu, B. A simple and concise synthesis of LY231514 (MTA). *Tetrahedron Lett.* **1999**, *40* (21), 4023–4026.

(78) Otterness, I. G.; Bliven, M. L. In *Nonsteroidal Anti-Inflammatory Drugs*; Lombardino, J. G., Ed.; Chemistry and Pharmacology of Drugs, Vol. 5; Wiley: New York, 1985; pp 111–252.

(79) Winter, C. A.; Risley, E. A.; Nuss, G. W. Carrageenan-induced edema in hind paw of rat as an assay for antiinflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544–547.

(80) Abraham, W. M.; Perruchoud, A. P. Role of arachidonic acid metabolites in allergen-induced late responses. *Respiration* **1989**, *56* (1–2), 48–56.

JM701467E