Inhibition of Cytosolic Phospholipase $A_2\alpha$: Hit to Lead Optimization

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Received August 10, 2005

Compound **1** was previously reported to be a potent inhibitor of $cPLA_2\alpha$ in both artificial monomeric substrate and cell-based assays. However, **1** was inactive in whole blood assays previously used to characterize cyclooxygenase and lipoxygenase inhibitors. The IC_{50} of **1** increased dramatically with cell number or lipid/detergent concentration. In an attempt to insert an electrophilic ketone between the indole and benzoic acid moieties, we discovered that increasing the distance between the two moieties gave a compound with activity in the GLU (7-hydroxycoumarinyl-γ-linolenate) micelle assay, which contains lipid and detergent. Extensive structure−activity relationship work around this lead identified a potent pharmacophore for $cPLA_2\alpha$ inhibition. The IC_{50}s between the GLU micelle and rat whole blood assays correlated highly. No correlation was found for other parameters, including lipophilicity or acidity of the required acid functionality. Compounds **25**, **39**, and **94** emerged as potent, selective inhibitors of $cPLA_2\alpha$ and represent well-validated starting points for further optimization.

Introduction

Arachidonic acid (AA) is released from cellular membranes by the action of a phospholipase A_2 to initiate the production of multiple mediators of inflammation, including prostaglandins (PG's) and leukotrienes (LT's). Nonsteroidal antiinflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors block the conversion of AA to prostaglandins (Figure 1), and extensive clinical trials have confirmed that prostaglandins are proinflammatory and potentiate pain.[1] Prostaglandins promote swelling and edema associated with inflammation through vasodilatation and increased vascular permeability and cause hyperalgesia by promoting the phosphorylation of ion channels in sensory neurons. The resulting modulation in ion channel activity increases the excitability and lowers the pain threshold of sensory neurons.[2,3] Leukotriene B_4 (LTB_4), a metabolite of 5-lipoxygenase (5-LO), and related arachidonate metabolites of 12-lipoxygenase also activate ion channels on neurons.[4] Furthermore, LTB_4 contributes to inflammation by both recruiting and activating leukocytes, and cysteinyl leukotrienes (LTC_4, D_4, and E_4) promote edema by increasing vascular permeability and permitting leakage of plasma to the extra vascular space.[5] Thus there may be added benefit in inhibiting both prostaglandins and leukotriene in the treatment of inflammation and pain.

Clinically, cysteinyl leukotriene receptor antagonists and 5-LO inhibitors have been shown to control asthma symptoms.[6−14] Prostaglandin D_2 (PGD_2) and thromboxane A_2 (TXA_2) have also been implicated in multiple aspects of allergic airway inflammation, promoting acute hyperresponsiveness (AHR) and allergic airway bronchoconstriction.[15−18] In contrast, prostaglandin E_2 (PGE_2), acting through the EP_2 receptor, may play a partially beneficial role in forms of asthma.[19]

The third class of lipid mediator generated following AA release is platelet activating factor (PAF). Although the lysophospholipid precursor for PAF could be generated from phospholipids containing other fatty acids in the sn-2 position, the release of AA and PAF synthesis are linked.[20−22] Although PAF receptor antagonists have not been successful in the clinic, genetically altered mice either overexpressing or deficient in the PAF receptor support a role for PAF in inflammation.[23] The effect of PAF may be difficult to antagonize, because inflamed endothelial cells synthesize and retain PAF at the cell surface, where it activates leukocytes in cooperation with other cell−cell interactions.[20] Thus, a PAF receptor antagonist must compete against PAF in the context of multiple cell−cell interactions. In contrast, a phospholipaseA_2 inhibitor would block the original synthesis of PAF.

Given the potential importance of inhibiting arachidonate release, numerous companies have attempted to develop phospholipase A_2 inhibitors. For many years the focus of these efforts was directed against the low molecular weight secretory phospholipase A_2 ($sPLA_2$)[24,25] with particular focus on the type II enzyme isolated from synovial fluid and later the type V enzyme. However, the role of these enzymes in prostaglandin and leukotriene production remains "ambiguous".[26] The type II enzyme is naturally deleted in multiple strains of mice commonly used in inflammatory models,[27] and potent inhibitors have been developed for these enzymes that do not have effects on eicosanoid production.[28]

The discovery of cytosolic phospholipase $A_2\alpha$[29−32] ($cPLA_2\alpha$, a group IVA phospholipase) generated a new target for therapeutic intervention. In contrast to $sPLA_2$, $cPLA_2\alpha$ shows selectivity for arachidonyl-containing glycerophospholipids, and agents that stimulate AA release also activate $cPLA_2\alpha$ by phosphorylation and mobilization of intracellular calcium.[31] These biochemical data strongly suggest that $cPLA_2\alpha$ is the phospholipase responsible for the selective generation of arachidonic acid in vivo. Gene-deleted mice have been prepared[33−36] and the data from these animals clearly bolster this case. When cells from these healthy animals are stimulated, prostaglandins,

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10.1021/jm0507882 CCC: $33.50
Published on Web 12/08/2005

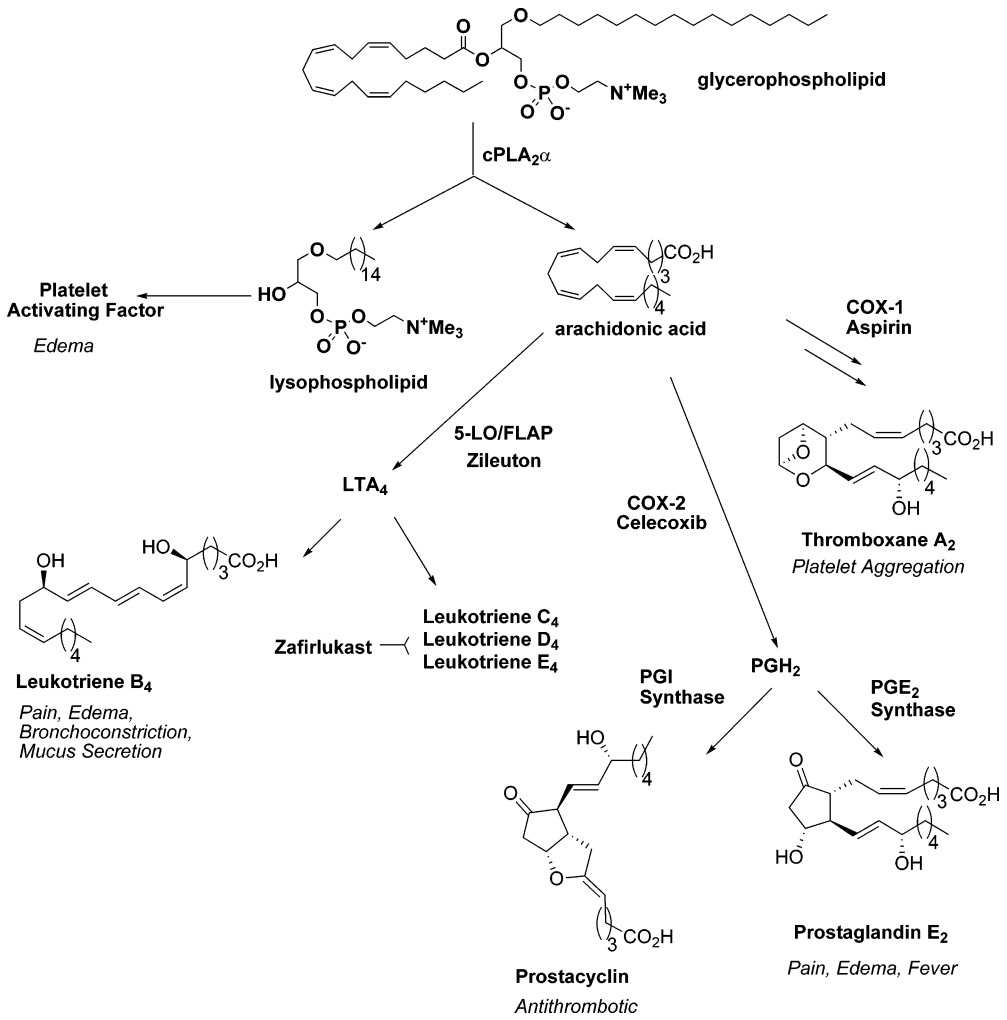


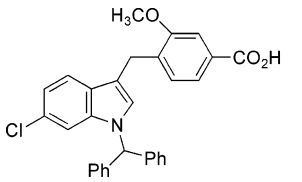
Figure 1. cPLA$_2\alpha$ initiates the production of multiple mediators of inflammation.

leukotrienes, and PAF are reduced by >90%. These mice are generally healthy and are also resistant to numerous inflammatory disease models, including collagen-induced arthritis,[37] an ova-induced model of anaphylaxis,[38] acid- or sepsis-induced adult respiratory distress syndrome (ARDS),[39] reperfusion injury in a model of middle cerebral artery occlusion,[34] the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced model of Parkinson's disease,[40−42] and polyp formation in APC (adenoma polyposis carcinoma) mice.[43,44] It is noteworthy that the effect of cPLA$_2\alpha$ deletion in the majority of these disease models is consistent with the behavior seen for gene deletions in the COX and 5-LO pathways.[45−47] Therefore, an inhibitor of cPLA$_2\alpha$ would be able to inhibit the production of leukotrienes, prostaglandins, and PAF and could provide a novel therapeutic with applications in many disease states, including pain, signs and symptoms of osteo- and rheumatoid arthritis, and asthma.

The past decade has seen the introduction of COX-2-specific inhibitors of prostaglandin synthesis to the market. COX-2 inhibitors do not inhibit normal gastric prostaglandin production and cause fewer serious GI complications than nonselective NSAIDs,[48,49] confirming the benefit of gastric PGE$_2$ synthesis. Although cPLA$_2\alpha$ inhibitors will act like NSAIDs in blocking both the COX-1 and COX-2 pathways, they would also inhibit the synthesis of leukotrienes, which are thought to promote ulceration in the absence of prostaglandins through both the recruitment and priming of neutrophils and by reducing blood flow to the gastric mucosa.[50−55] Thus, the concurrent inhibition of leukotrienes may ameliorate the effects of gastric prostaglandin inhibition. In support of this hypothesis, dual COX/5-LO inhibitors are nonulcerogenic.[56]

Although the COX-2 inhibitors appear safer for the digestive tract of chronic users, they may carry a greater risk to the cardiovascular system.[1,57−61] For example, the COX-1-derived prostaglandin TXA$_2$ is a potent activator of platelet aggregation. The selective inhibition of platelet-derived thromboxane production is thought to be the underlying mechanism for the cardiovascular benefit of aspirin, and the lack of thromboxane inhibition coupled with inhibition of endothelial-derived prostacyclin may be linked to the clot-related cardiovascular events noted for COX-2 inhibitors.[62,63] In contrast to COX-2 inhibitors, inhibitors of cPLA$_2\alpha$ will block COX-1-dependent thromboxane synthesis. Thus a cPLA$_2\alpha$ inhibitor would offer potential advantages due to the inhibition of both thromboxane and prostacyclin synthesis.

Inhibitors of cPLA$_2\alpha$ have been reported previously.[64] These inhibitors range from electrophilic ketones, such as the trifluoromethyl ketone of arachdonic acid,[65−69] to natural products[70,71] that inhibit cPLA$_2\alpha$, to compounds that are purported to have dual[72] cPLA$_2\alpha$ and sPLA$_2$ activity. Merckle[73−75] disclosed one of the first series of compounds thought to be inhibitors of cPLA$_2\alpha$. Elan[76] has patented a group of cPLA$_2\alpha$ inhibitors generated from pyrimidones. Shionogi[77−80] has reported on a series of pyrrolidine-based inhibitors that are among the most potent cPLA$_2\alpha$ inhibitors disclosed. Since the Shionogi compounds are the only inhibitors above-reported to have activity in whole blood assays, they appear to be the compounds



1
Coumarin IC_{50} = 0.8 μM
MC-9 IC_{50} LTB_4 = 0.8 μM
%F rat = 63

Figure 2. Data summary for $cPLA_2\alpha$ hit **1**.

with the best chance for efficacy in in vivo models of inflammation; however no data have been reported.

Evaluation of Biological Assays. Previously we had reported on a class of indole inhibitors of $cPLA_2\alpha$ that were designed using a substrate mimetic approach[81] and an assay scheme used to evaluate these inhibitors. $cPLA_2\alpha$ 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 this system, compounds interfering with any of these parameters score as inhibitors. Although excellent $sPLA_2$ assay systems were developed, where essentially all $sPLA_2$ was bound at the membrane surface in order to simplify the kinetics,[82] analogous systems for $cPLA_2\alpha$ were problematic because $cPLA_2\alpha$ inactivated at an unpredictable rate.[83] Therefore the original inhibitors were optimized using an artificial monomeric substrate, 2-oxo-2*H*-chromen-6-yl hept-6-enoate.[84] Although we could not saturate the enzyme with the coumarin substrate before it formed an aggregate, the assay appeared to be less prone to false inhibitors that worked by disrupting the membrane.

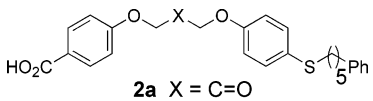
Optimization delivered compounds that were active in both the soluble substrate coumarin assay, and in an MC-9 cell based assay[85] monitoring downstream leukotriene products. This class of molecules is exemplified by **1** (Figure 2), which also has appropriate pharmacokinetic properties for consideration as a lead for further optimization. A model of **1** docked into the published crystal structure of $cPLA_2\alpha$ indicated that the benzoate functionality extended partially into the active site pocket, where it could interact with the postulated phosphate-binding pocket, and the benzhydryl group formed an interaction with the underside of the α-helical lid that partially covers the active site. Assays of increasing complexity and physiological relevance were examined to more fully understand the interaction of this inhibitor with $cPLA_2\alpha$.

Following the lead of previous 5-LO and COX programs, we recognized the utility of a whole blood assay to predict efficacy both clinically and preclinically. However, **1** and other compounds in the class were inactive in a calcium ionophore (A23187) stimulated rat whole blood assay using the downstream readout TXB_2, which is a metabolite of TXA_2. Under these conditions, the inhibitor showed an IC_{50} higher than 400 μM. This level of activity could be due to serum albumin binding, partitioning of the compound into the extensive amount of lipid membrane present in blood, or both. When the cells in the whole blood assay were pelleted by centrifugation, washed with buffered saline, and stimulated to produce thromboxane,

Table 1. Activity of **1** in Assays of Increasing Complexity

	IC_{50} (μM) of **1**
MC-9 LTB_4, 1×10^6 cells/mL	0.8
MC-9 LTB_4, 4×10^6 cells/mL	1.5
MC-9 LTB_4, 8×10^6 cells/mL	8.3
GLU micelle	160
rat WB TXB_2	>400

Table 2. Summary of Data for Inhibitors **2a** and **2b**



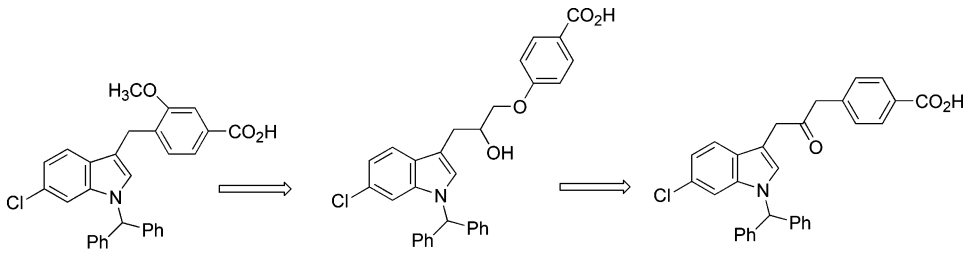
2a X = C=O
2b X = HCOH

	IC_{50} (μM)	
	2a	**2b**
GLU micelle	0.04	340
MC-9 LTB_4, 4×10^6 cell/mL	1.5	NT
rat WB TXB_2	12	>100
Coumarin	1	20

1 remained essentially inactive, implying that the compound was inactive in the presence of high amounts of cellular lipid. With this knowledge, the MC-9 assay was reexamined by varying the cell density and it quickly became evident from the data presented in Table 1 that the IC_{50} is dependent upon the conditions in which the assay is run. Higher cell counts, with a greater concentration of lipid membranes, significantly shifted the IC_{50} upward. Similarly, **1** was inactive when an analogue of the coumarin substrate containing 2-oxo-2*H*-chromen-6-yl (6*Z*,9*Z*,12*Z*)-octadeca-6,9,12-trienoate (7-hydroxy-coumarinyl-γ-linolenate or GLU)[84] in place of the 2-oxo-2*H*-chromen-6-yl hept-6-enoate was presented to the enzyme in a micelle containing ∼1 mM Triton X-100 and phospholipid. Clearly, the soluble substrate assay was not predictive of activity in assays that contained more detergent or high cell number. Therefore, the assay scheme that was chosen to evaluate additional analogues synthesized was the GLU micelle assay followed by the rat whole blood assay. It was predicted that these two stringent assays would result in a structure−activity relationship (SAR) that was relevant to preparation of potential drug candidates. Significant effort was now required to convert the hit **1** into a lead for analogue development.

At this time an interesting $cPLA_2\alpha$ presentation from AstraZeneca disclosed a class of electrophilic ketone-based $cPLA_2\alpha$ inhibitors.[86,87] There is long history of using electrophilic ketones to inhibit $cPLA_2\alpha$, as well as serine proteases, in the literature. While these compounds are potent under some assay conditions, they are plagued by reduction of the electrophilic ketone functionality and subsequent loss of potency under more physiological conditions.[88] This class of inhibitor caught our attention because it showed exceptional potency in the GLU micelle assay, as shown in Table 2. Compound **2a** shows reduced potency in the cell-based assay as well as much reduced activity in whole blood. The ketone functionality is essential for activity, as demonstrated by the complete lack of activity of the hydroxyl analogue **2b**. Neither of these analogues would have been viewed as potent inhibitors on the basis of the coumarin assay data.

The strategy utilized to increase the potency of **1** in the GLU assay was to attempt to incorporate an electrophilic ketone into the C_3 linker. This strategy is depicted in Figure 3. Alcohol **3** was an intermediate in the preparation of the ketone (Scheme 1) and was to be used as a negative control. Contrary to our

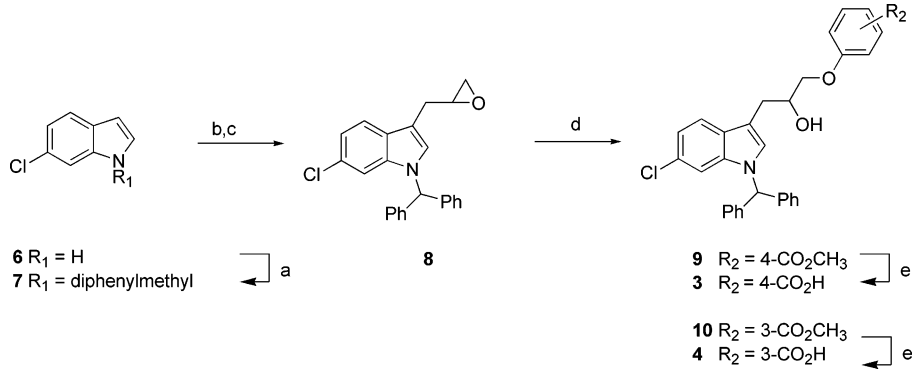


1 **3**

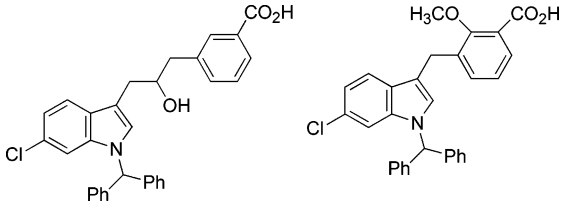
	3 IC_{50} (μM)
GLU Micelle	40
Rat WB TXB_2	100

Figure 3. Incorporation of an electrophilic ketone into **1**.

Scheme 1. Synthetic Route for **3** and **4**[a]



[a] (a) NaH, Ph_2CHBr, DMF; (b) epibromohydrin, $SnCl_4$, 0 °C; (c) NaH, DMF; (d) KO-*t*Bu, ArOH, MeOH, DMF; (e) NaOH, THF, MeOH.



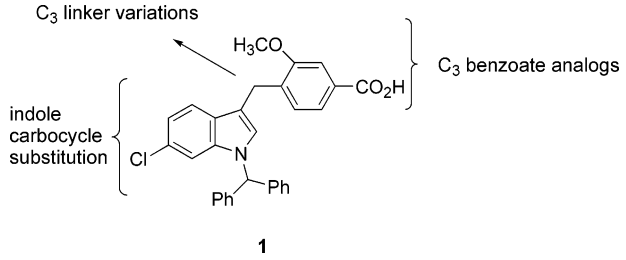
4 **5**

	4 IC_{50} (μM)	5 IC_{50} (μM)
GLU Micelle	90	120

Figure 4. *m*-Benzoic acid analogues.

expectations, **3** was significantly more potent (Figure 3) than **1** and showed weak but reproducible activity in the whole blood assay. Clearly this activity was not due to the presence of an electrophilic ketone and it was postulated that it arose simply from increasing the distance between the carboxylic acid moiety and the indole template.

Some evidence that a more specific interaction is being made with the extended acid is shown by comparing the corresponding *m*-carboxylic acids analogues **4** and **5** shown in Figure 4. In the GLU assay **5** is almost equipotent with the *p*-carboxylic acid **1**, while **4** is 2-fold less potent than **3**. This was interpreted as evidence of a more specific interaction between inhibitors with a longer C_3 linker and the enzyme. These initial analogues provided data that this assay scheme would provide valuable feedback for analogue creation and that increases in potency in the GLU assay could be reflected in the rat whole blood assay.

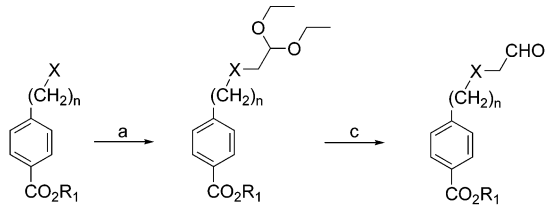


1

Figure 5. Areas targeted for analogue synthesis around **1**.

Chemistry: A variety of different synthetic strategies were employed to explore the SAR around this indole-based group of inhibitors. The exploration of SAR required synthetic routes[89] that allowed functionalization of the C_3 linker, the benzoate group at C_3, as well as the indole carbocycle (Figure 5). Earlier SAR had indicated that the *N*-benzhydryl group was needed for activity and as such it was kept constant. Primarily these analogues were built up from intact indoles whenever possible, and the indoles were in turn C_3 functionalized with a variety of electrophilic reagents, for example, epibromohydrin (Scheme 1), aldehydes (Schemes 3 and 4), oxalyl chloride and its derivatives (Schemes 9, 15, 17), alkyl halides (Scheme 7), bromo esters (Scheme 8), and Michael acceptors (Scheme 14). Several approaches that lead to late stage intermediates for varying the benzoate portion where devised (Schemes 12 and 18). Indole carbocycle variations that were not commercially available were synthesized by the Fischer indole reaction[90] followed by appropriate functionalization at C_3. Another synthetic route that provided a late-stage intermediate for varying the indole carbocycle via palladium-mediated coupling reactions was explored (Scheme 16).

Scheme 2. Synthesis of Aldehydes for Indole C_3 Reductive Alkylation[a]



11 R_1 = Me, X = OH, n= 0 **14** R_1 = Me, X = O, n = 0 **18** R_1 = Me, X = O, n = 0
12 R_1 = H, X = SH, n= 0 **15** R_1 = H, X = S, n = 0 **19** R_1 = Me, X = S, n = 0
16 R_1 = Me, X = S, n = 0
13 R_1 = Me, X = SH, n= 2 **17** R_1 = Me, X = S, n = 2 **20** R_1 = Me, X = S, n = 2

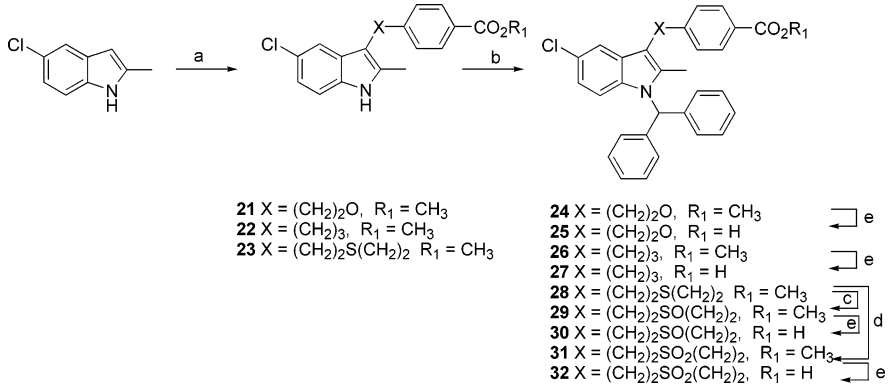
[a] (a) Base, DMF, 2-bromo-1,1-diethoxyethane; (b) oxalyl chloride, MeOH; (c) TFA, chloroform, H_2O.

Scheme 1 details the synthetic approach to compounds **3** and **4**, compounds that showed a significant improvement in activity upon extending the C_3 acid linker. 6-Chloroindole was N-alkylated with bromodiphenylmethane and the resulting indole was treated with tin tetrachloride and epibromohydrin to effect epoxide ring opening. The halo alcohol was then cyclized to an epoxide by treatment with sodium hydride and subsequently opened with the desired phenoxide. The esters were then hydrolyzed to generate the desired acids **3** and **4**.

A more general synthesis of C_3 analogues is shown in Scheme 3. Indoles were treated with various aldehydes under reductive alkylation conditions[91,92] to yield C_3 analogues in generally good yields. The products were then N-alkylated with bromodiphenylmethane. The analogues containing a thioether were then oxidized to the corresponding sulfoxides and sulfones, and finally all of the esters were hydrolyzed to the desired carboxylic acids. The aldehydes were either commercially available or synthesized (Scheme 2).

This reaction sequence is versatile enough to also be performed on the N-alkylated indoles (Scheme 4), which were then converted into the desired acids. When 5-chloro-2-methylindole is N-alkylated with benzhydryl bromide, an inseparable mixture of **33** and 1,3-bis dialkylated material was obtained. The reductive alkylation procedure was performed on this material and yielded pure desired product after a chromato-

Scheme 3. Indole Analogue Synthesis via Reductive Alkylation with Indole NH Substrates[a]

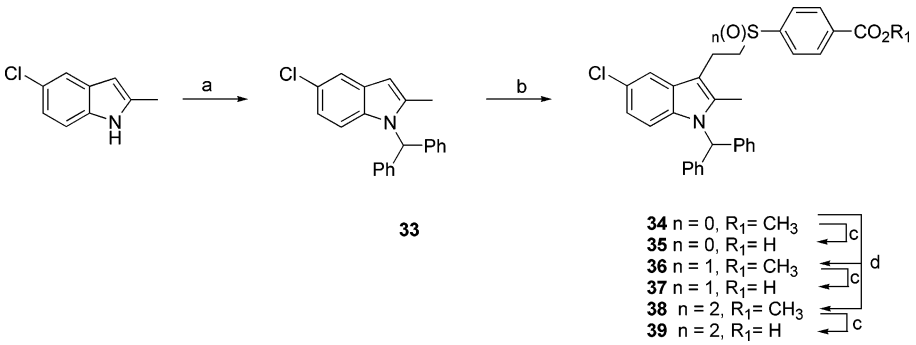


21 X = $(CH_2)_2O$, R_1 = CH_3
22 X = $(CH_2)_3$, R_1 = CH_3
23 X = $(CH_2)_2S(CH_2)_2$ R_1 = CH_3

24 X = $(CH_2)_2O$, R_1 = CH_3
25 X = $(CH_2)_2O$, R_1 = H
26 X = $(CH_2)_3$, R_1 = CH_3
27 X = $(CH_2)_3$, R_1 = H
28 X = $(CH_2)_2S(CH_2)_2$ R_1 = CH_3
29 X = $(CH_2)_2SO(CH_2)_2$, R_1 = CH_3
30 X = $(CH_2)_2SO(CH_2)_2$, R_1 = H
31 X = $(CH_2)_2SO_2(CH_2)_2$, R_1 = CH_3
32 X = $(CH_2)_2SO_2(CH_2)_2$, R_1 = H

[a] (a) RCHO, TFA, Et_3SiH; (b) NaH, Ph_2CHBr; (c) H_2O_2, acetone; (d) NMO, TPAP; (e) NaOH, MeOH, THF.

Scheme 4. Indole Synthesis via Reductive Alkylation with *N*-Alkyl Substrates[a]

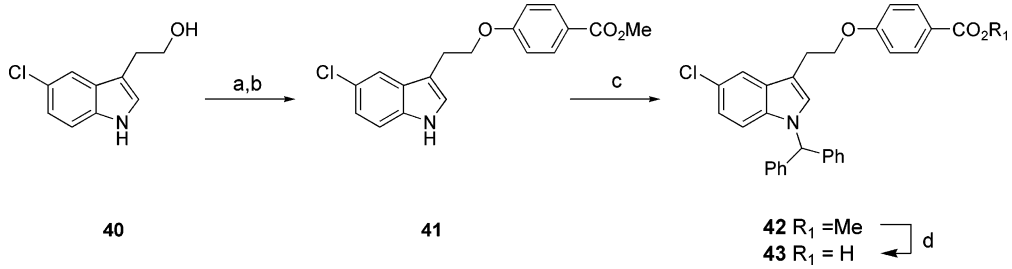


33

34 n = 0, R_1= CH_3
35 n = 0, R_1= H
36 n = 1, R_1= CH_3
37 n = 1, R_1= H
38 n = 2, R_1= CH_3
39 n = 2, R_1= H

[a] (a) NaH, Ph_2CHBr; (b) RCHO, TFA, Et_3SiH; (c) NaOH, MeOH, THF; (d) Oxone, MeOH, H_2O.

Scheme 5. C_2 Unsubstituted Analogues[a]

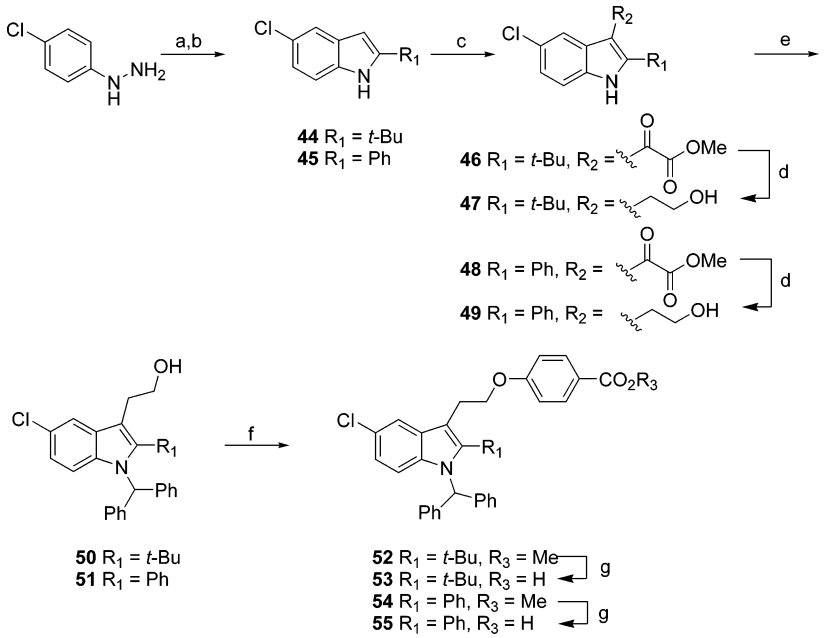


40 **41**

42 R_1 =Me
43 R_1 = H

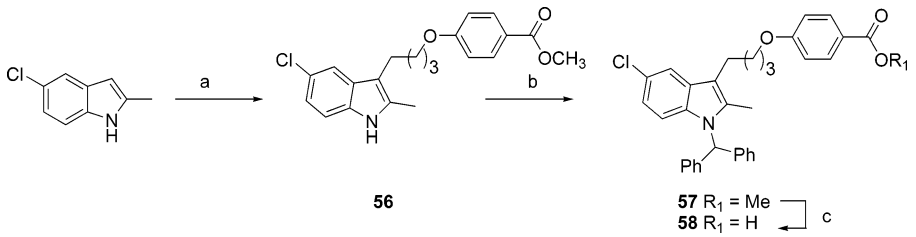
[a] (a) MsCl, triethylamine, CH_2Cl_2; (b) methyl 4-hydroxybenzoate, NaH, DMF; (c) NaH, DMF, Ph_2CHBr; (d) NaOH, THF, MeOH.

Scheme 6. Synthesis of C_2 Analogues[a]



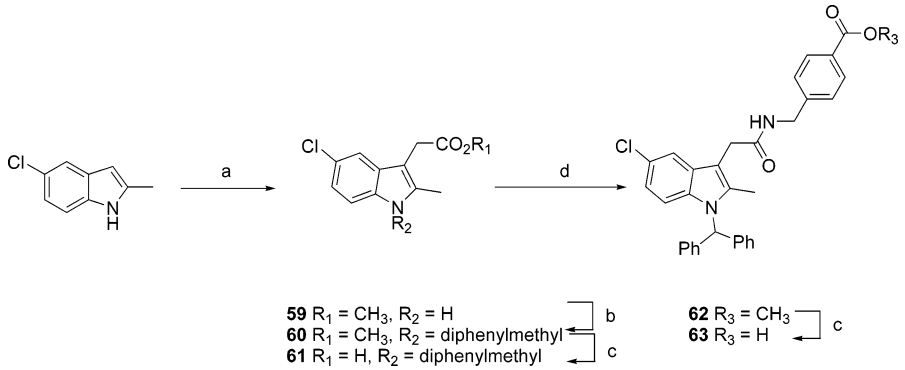
[a] (a) $NaHCO_3$, CH_2Cl_2, 3,3-dimethylbutan-2-one for **44** and 1-phenylethanone for **45**; (b) $ZnCl_2$, 140 °C; (c) oxalyl chloride, MeOH; (d) $LiAlH_4$, THF; (e) NaH, DMF, Ph_2CHBr; (f) methyl 4-hydroxybenzoate, PPh_3, DIAD, CH_2Cl_2; (g) NaOH, THF, MeOH.

Scheme 7. Indole C_3 Alkylation with an Alkyl Bromide[a]



[a] (a) (i) *n*-BuLi, THF, 10 °C, $ZnCl_2$ in Et_2O, (ii) methyl 4-(4-bromobutoxy)benzoate, rt; (b) NaH, DMF, Ph_2CHBr; (c) NaOH, MeOH, THF.

Scheme 8. C_3 Functionalization To Yield Amide-Linked Analogues[a]



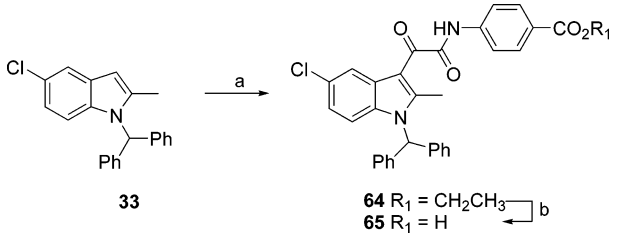
[a] (a) (i) *n*-BuLi, THF, 10 °C, $ZnCl_2$ in Et_2O, (ii) methyl bromoacetate; (b) NaH, DMF, Ph_2CHBr; (c) NaOH, MeOH, THF; (d) methyl 4-aminomethylbenzoate, EDCI, DMAP, DMF, rt.

graphic separation. This approach allowed us to rapidly explore C_3 variations as shown in Scheme 4 to yield **35**, **37**, and **39**.

An approach to C_2 unsubstituted analogues such as **43** began with the known **40**,[93] which was converted to the mesylate and then displaced with a phenoxide. N-Alkylation with bromodiphenylmethane and ester hydrolysis yielded the desired acid, as shown in Scheme 5.

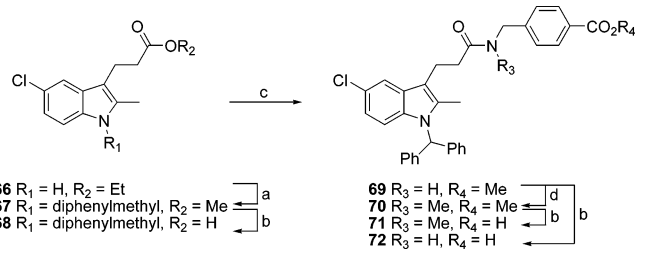
Variation of the size of the substituent at C_2 was also explored using a Fischer indole synthesis followed by C_3 oxalate formation, reduction to the primary alcohol, Mitsunobu reaction to install the benzoate, and then hydrolysis to the desired benzoic

Scheme 9. Approach To Generate Oxamide Linked C_3 Analoues[a]



[a] (a) Oxalyl chloride, CH_2Cl_2, ethyl 4-aminobenzoate; (b) NaOH, MeOH, THF.

Scheme 10. Extended Amide-Linked Analogues[a]



[a] (a) NaH, DMF, Ph_2CHBr; (b) NaOH, MeOH, THF; (c) methyl 4-aminomethylbenzoate, EDCI, DMAP, DMF, rt; (d) NaH, DMF, methyl iodide.

acids. The synthetic routes in Schemes 4 and 6 allowed the C_2 unsubstituted, Me, Ph, and *t*-Bu analogues to be synthesized.

Another strategy to functionalize the indole C_3 position lies in reacting the zinc salt of the indole with a primary bromide.[94,95] The resulting compound was then N-alkylated with bromodiphenylmethane and hydrolyzed to yield the desired carboxylic acid. An example of this approach is shown in Scheme 7 for the synthesis of **58**.

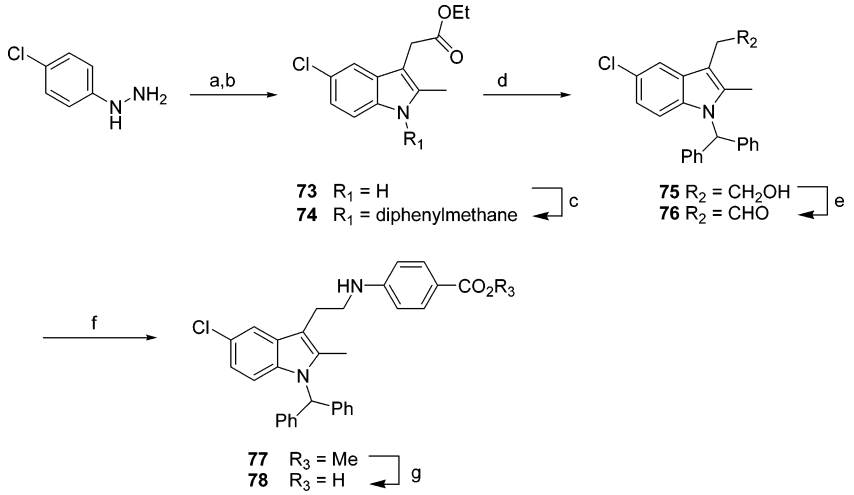
This same methodology could be employed with methyl bromoacetate as the electrophile. The resulting indolyl methyl acetate was N-alkylated with bromodiphenylmethane and then hydrolyzed to the carboxylic acid. This was followed by a carbodiimide coupling reaction with methyl 4-aminomethyl benzoate and finally hydrolysis to yield the desired carboxylic acid **63** (Scheme 8).

Another approach was to treat **33** (Scheme 4) with oxalyl chloride followed by allowing the resulting oxo-acetyl chloride to react with an amino ester that was subsequently hydrolyzed to the target **65** (Scheme 9).

C_3 derivatives with amide linkers could be accessed by subjecting known **66**[96] to N-alkylation with bromodiphenylmethane. The resulting ester was hydrolyzed and then subjected to a carbodiimde coupling with methyl 4-aminobenzoate. Some of this ester was N-alkylated with methyl iodide, and then both derivatives were hydrolyzed to the carboxylic acids **71** and **72** (Scheme 10).

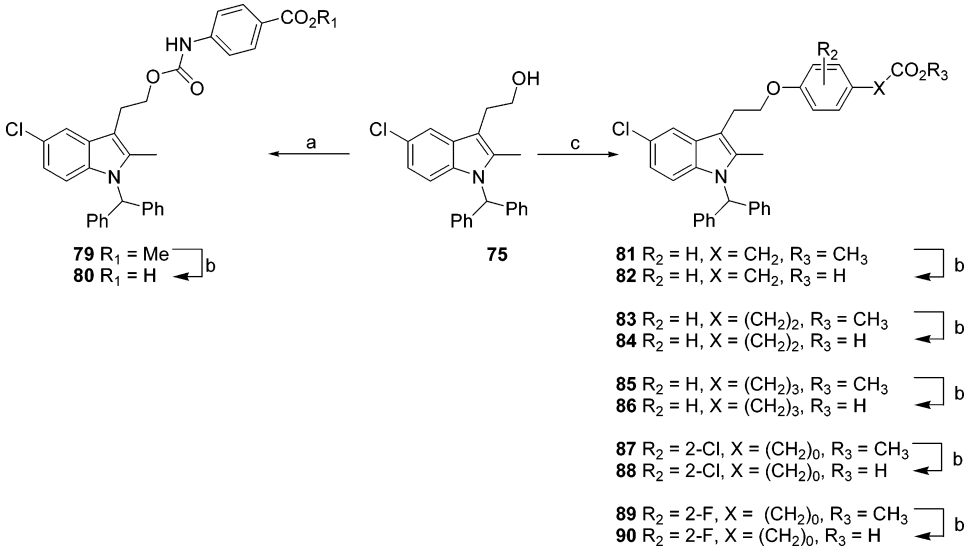
An analogue with an amino linker at C_3 was obtained via a Fischer indole cyclization between 4-chlorophenyl hydrazine and ethyl levulinate followed by N-alkylation with bromodiphenylmethane. The resulting ester was reduced to alcohol **75**,

Scheme 11. Fischer Indole Approach To Yield C_3 Amino-Linked Analogues[a]



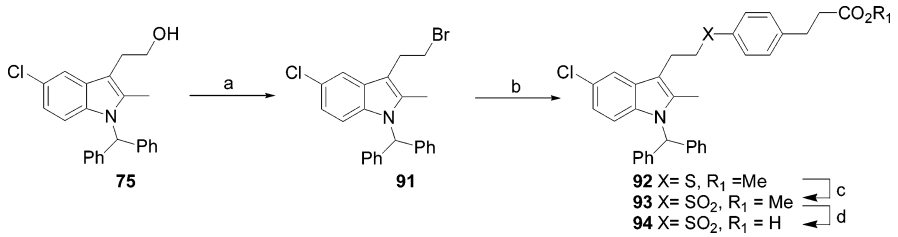
[a] (a) Ethyl levulinate, aq $NaHCO_3$, CH_2Cl_2; (b) $ZnCl_2$, 140 °C; (c) NaH, DMF, Ph_2CHBr; (d) $LiAlH_4$, THF, 0 °C; (e) Dess−Martin periodinane, CH_2Cl_2; (f) methyl 4-aminobenzoate, sodium cyanoborohydride; (g) NaOH, MeOH, THF.

Scheme 12. C_3 Analogues via Alcohol 75[a]



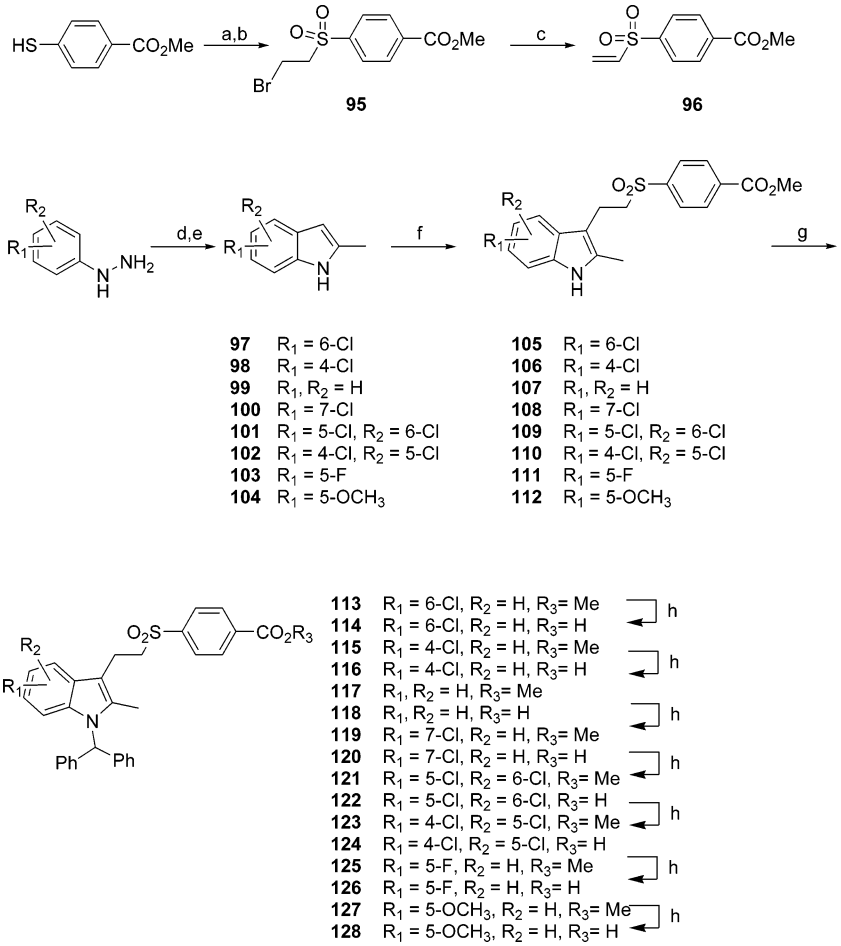
[a] (a) Ethyl 4-isocyanatobenzoate; (b) NaOH, MeOH, THF; (c) ArOH, polystyrene-bound PPh_3, DIAD, CH_2Cl_2.

Scheme 13. Synthetic Approach To Install a Sulfone Containing Linker at C_3[a]



[a] (a) CBr_4, 1,3-bis(diphenylphosphino)propane, CH_2Cl_2; (b) methyl 3-(4-mercaptophenyl)propanoate, K_2CO_3, DMF; (c) TPAP, NMO, 4-Å sieves, CH_3CN, 40 °C; (d) NaOH, MeOH, THF.

Scheme 14. Synthetic Scheme To Vary the Indole Carbocycle[a]



[a] (a) K_2CO_3, dibromoethane, DMF; (b) aq Oxone, acetone, MeOH; (c) NEt_3, CH_2Cl_2; (d) $NaHCO_3$, CH_2Cl_2, acetone; (e) $ZnCl_2$, 140 °C; (f) *n*-BuLi, THF, −78 °C, $ZnCl_2$, −78 °C to rt, **96**; (g) NaH, DMF, Ph_2CHBr 0 °C to rt; (h) NaOH, THF, MeOH.

which was oxidized to the aldehyde, reacted with methyl 4-aminobenzoate,[97] and then hydrolyzed to yield the desired acid **78** (Scheme 11).

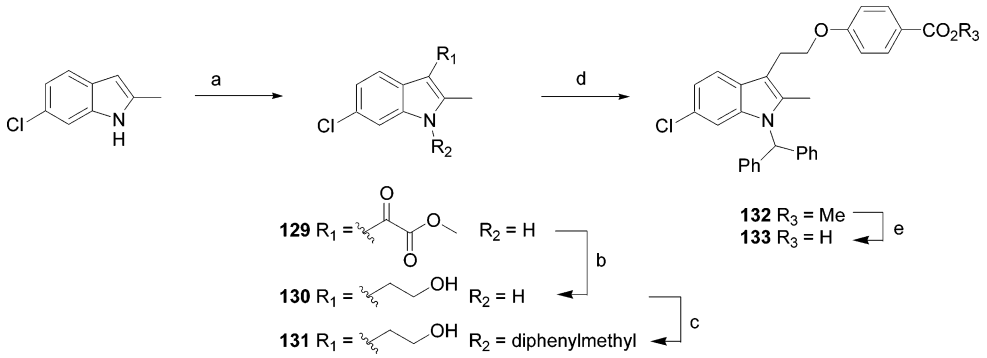
Alcohol **75** from Scheme 11 could be used as a valuable late-stage intermediate by reaction with ethyl 4-isocyanatobenzoate followed by conversion to the desired acid as shown in Scheme 12. Alternatively, this alcohol could be subjected to Mitsunobu conditions to install a variety of benzoate linker modifications (Scheme 12).

Installation of a sulfone linker at C_3 was accomplished by converting **75** first to a bromide and then by displacement with a thiophenol nucleophile. Ester **92** was then oxidized to the sulfone and finally hydrolyzed to yield **94** (Scheme 13).

To examine specific changes to the indole carbocycle, analogues were proposed that kept the C_3 sulfone benzoate substituent constant. Since changes in the indole are present from the beginning of the synthesis, a convergent three-step process to final compounds was devised. Because not all of the desired substituted indoles were available commercially, the Fischer indole synthesis was again utilized. In several cases mixtures of products were generated from the Fischer route and these were separated and carried through for additional SAR points. The resulting indoles were functionalized at C_3 by treating the indole zinc salt with the vinyl sulfone **96**. Despite a paucity of reports using the vinyl sulfone as an electrophile, it generated the C_3-elaborated compounds in moderate yield. These analogues were then N-alkylated with bromodiphenylmethane, without any alkylation of the carbon α to the sulfone. Finally, these esters could be hydrolyzed to the desired acids (Scheme 14).

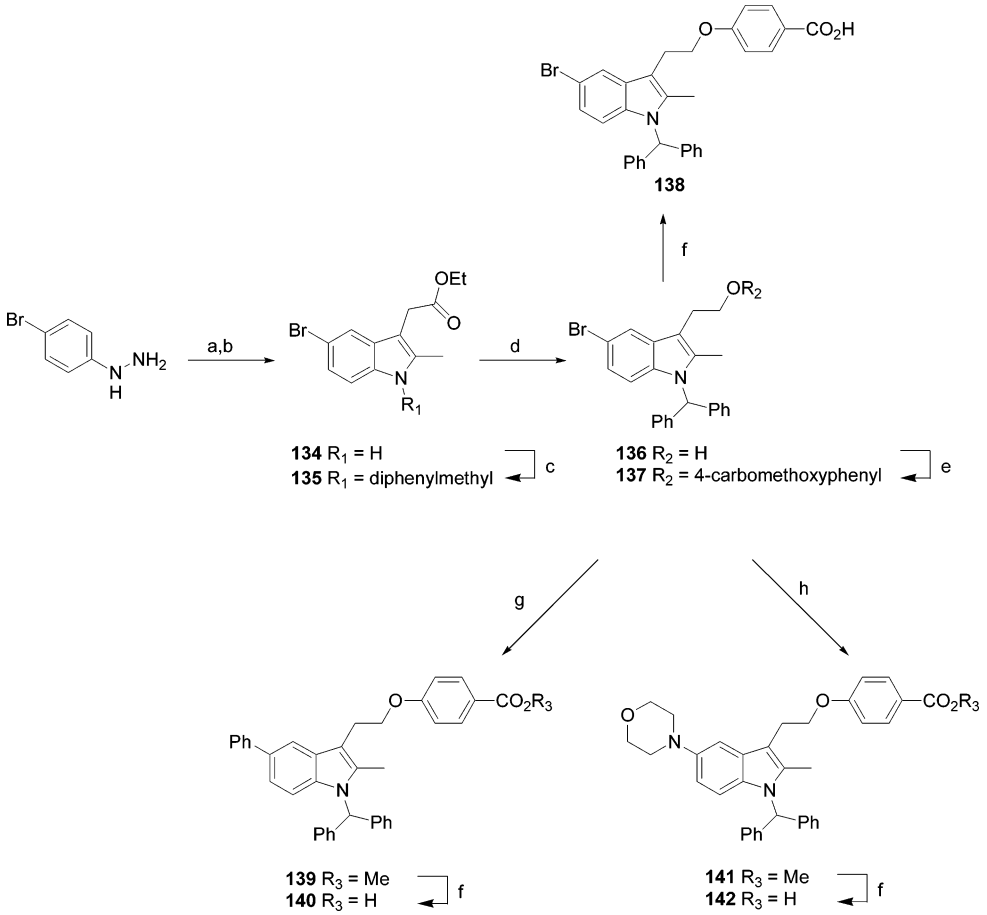
Indole carbocycle analogues with a three-atom oxygen-containing C_3 linker were derived from three different routes.

Scheme 15. Carbocycle Modification with Oxygen Linker to Benzoate[a]



[a] (a) Oxalyl chloride, ether and then MeOH; (b) $LiAlH_4$, THF; (c) NaH, DMF, Ph_2CHBr; (d) methyl 4-hydroxybenzoate, PPh_3, DIAD, CH_2Cl_2; (e) NaOH, MeOH, THF.

Scheme 16. Late-Stage Indole Carbocycle Modifications Using Pd Coupling Conditions[a]

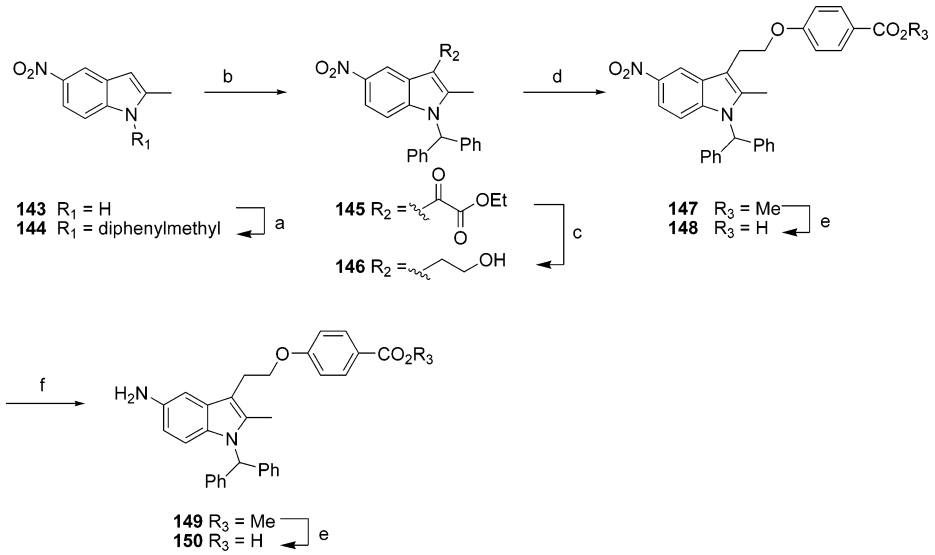


[a] (a) Ethyl levulinate, aq sodium bicarbonate, CH_2Cl_2; (b) $ZnCl_2$, 140 °C; (c) NaH, DMF, Ph_2CHBr; (d) $LiAlH_4$, THF, 0 °C; (e) methyl 4-hydroxybenzoate, polystyrene-bound PPh_3, DIAD, CH_2Cl_2; (f) NaOH, MeOH, THF; (g) phenylboronic acid, $Pd(OAc)_2$, biphenyl-3-yldi-*tert*-butylphosphane, KF, THF; (h) tris(dibenzylideneacetone)dipalladium(0), biphenyl-3-yldi-*tert*-butylphosphane, sodium *tert*-butoxide, morpholine, toluene, 80 °C.

Scheme 15 details the synthesis of **133**, where the commercially available indole is C_3-functionalized with oxalyl chloride followed by methanol. The oxoacetate was reduced, the indole then was N-alkylated with bromodiphenylmethane, which was in turn subjected to Mitsunobu conditions with methyl 4-hydroxybenzoate, and then ester hydrolysis generated the desired acid. Another method to generate diversity in the carbocycle of the indole is shown in Scheme 16. Here ethyl (5-bromo-2-methyl-1*H*-indol-3-yl)acetate is constructed through a Fischer indole[90] route using ethyl levulinate. The ester is N-alkylated, reduced, and then treated under Mitsunobu[98] conditions with methyl 4-hydroxybenzoate. This ester could be hydrolyzed to yield the acid **138** or subjected to palladium coupling conditions[99] with phenyl boronic acid or palladium-catalyzed amination conditions[100] with morpholine. Hydrolysis of the resulting esters generated **140** and **142**. A third variation starts with 2-methyl-5-nitroindole, which was N-alkylated, C_3-elaborated using ethyl chloro(oxo)acetate, and subsequently reduced and subjected to the Mitsunobu reaction with methyl 4-hydroxybenzoate. A portion of ester **147** was reduced and then the nitro and amino esters were hydrolyzed to yield the corresponding acids **148** and **150** (Scheme 17).

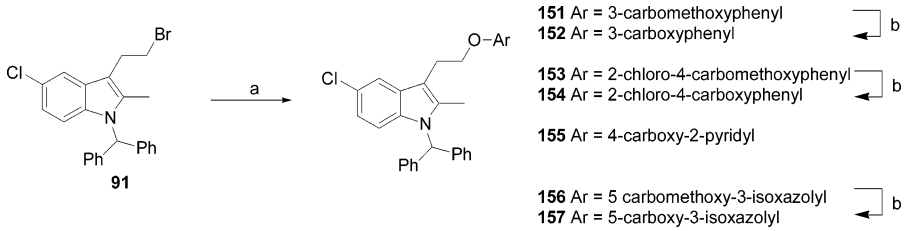
Another synthetic approach from a late-stage intermediate that allowed both variations to the benzoate headgroup and the construction of a three-atom amino linker is shown in Scheme 18. Bromide **91** (Scheme 13) was reacted with a variety of

Scheme 17. Synthesis of 5-Nitro and 5-Amino Indole Analogues[a]



[a] (a) NaH, DMF, Ph_2CHBr; (b) ethyl chlorooxoacetate, $AlCl_3$, CH_2Cl_2; (c) BH_3SMe_2, THF, reflux; (d) methyl 4-hydroxybenzoate, polystyrene-bound PPh_3, DIAD, CH_2Cl_2; (e) NaOH, MeOH, THF; (f) Pd on carbon (10 wt %), H_2.

Scheme 18. Synthetic Route to Benzoate Analogues[a]



[a] (a) NaH, DMF, ArOH; (b) NaOH, MeOH, THF.

phenoxides that were then hydrolyzed to the desired acids **152**, **154**, **155**, and **157**.

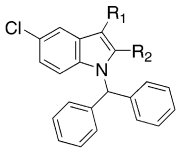
Medicinal Chemistry Results and Discussions. The strategy to explore the SAR around **3** centered on examining the contribution of the linker to potency and to determine the optimal substituent at C_2. The results from these analogues are presented in Table 3. A phenolic oxygen linker (see **25** and **43**) clearly demonstrates that simple extension of the linker without any polarity is enough to significantly enhance activity. This pair also shows that the C_2 methyl analogues are more potent than the C_2 unsubstituted analogues by 2-fold. The C_2 substituent was further explored in **52** and **55**. Both the C_2 phenyl and C_2 *tert*-butyl analogues resulted in a significant loss in potency. For the remaining analogues, the C_2 methyl was held constant. An all-carbon linker at C_3 resulted in compound **27**, equipotent to **25**. Substitution of S for O generated **35**, which was again equipotent to **25**. More exciting was that the sulfoxide and sulfone analogues showed increased potency; in fact, **39** was the first sub-micromolar inhibitor in this series. Substitution of an amine, **78**, at this position, however, led to a substantial decrease in potency. Longer linkers were well-tolerated (compare **58** and **25**), except when polar groups were introduced in the linker. Sulfones, sulfoxides, amides, ketoamides, and carbamates (**32**, **30**, **61**, **70, 72**, **65**, **80**) all showed attenuated potency. Keeping the linker length between the indole and phenyl ring constant and moving the carboxylic acid further away from the phenyl group indicated that perhaps two distinct specific COOH interactions were possible. One- and three-carbon extensions, **82** and **86**, led to much less potent analogues, whereas a two-carbon linker (**84** and **94**) led to slight increases in potency. Compound **94** represents a major advance in that it is the first compound that showed sub-micromolar activity in the rat whole blood assay.

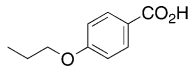
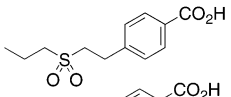
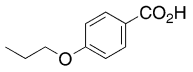
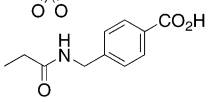
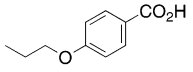
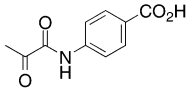
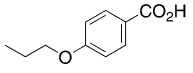
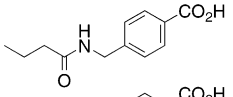
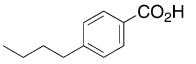
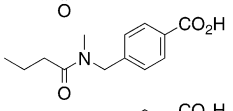
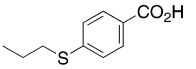
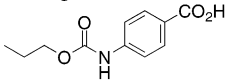
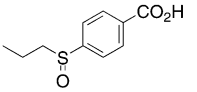
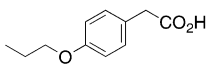
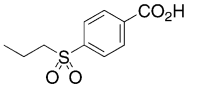
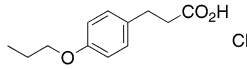
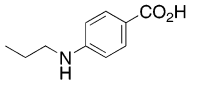
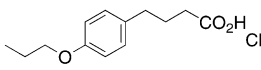
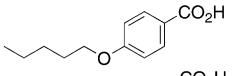
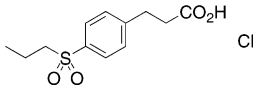
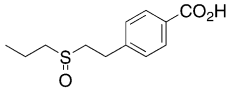
The next phase of the optimization focused on variations to the indole carbocycle substituent, and these analogues are presented in Table 4. It was quickly determined that small substituents at the 5 position were the most potent (eg, **25**, **39** and **126**), irrespective of the linker at C_3. Substitution of chloro at any other position in the ring or leaving the ring unsubstituted resulted in a 2−9-fold decrease in potency, cf. **133**, **116**, **120**, and **118**. Disubstitution either at C_5 and C_6 (**122**) or C_4 and C_5 (**124**) also resulted in reduced potency. Electron-withdrawing groups bigger than a chloro were well-tolerated but the amino- and methoxy-substituted analogues **150** and **128** were much less potent. The biggest change in potency resulted from incorporation of the phenyl (**140**) or morpholino (**142**) substituents; these large substituents resulted in a 10-fold loss in activity.

While the 5-chloro-2-methyl-*N*-benzhydrylindole template was maintained, larger variations to the benzoic acid group were next examined and are tabulated in Table 5. Simply moving the acid from para to meta resulted in a 40-fold loss in activity, cf. **25** to **152**. Substitution of a chloro ortho to the linker (**154**) or meta to the linker (**88**) resulted in a decrease of potency. Fluoro substitution ortho to the acid (**90**) was equipotent with **25**. Finally, substitution of the phenyl ring by either pyridyl (**155**) or oxazolyl (**157**) resulted in a substantial loss in potency.

Several analogues clearly stand out with respect to potency: **25**, **39**, and **94**. These analogues were subjected to a modification of the MC-9 cell based assay to confirm they were selective inhibitors of $cPLA_2\alpha$ without activity on downstream enzymes in the prostaglandin biosynthesis pathway (Figure 1). These MC-9 data are presented in Table 6, and they demonstrate that

Table 3. Linker Variation



Compd	R_1	R_2	IC_{50} (μM) GLU micelle	IC_{50} (μM) Rat WB TXB_2	Compd	R_1	R_2	IC_{50} (μM) GLU micelle	IC_{50} (μM) Rat WB TXB_2
25		CH_3	3	7	**32**		CH_3	93	14
43		H	5	14	**61**		CH_3	165	<100
52		*t*-Bu	20	>25	**65**		CH_3	26	25
55		Ph	>50	>50	**70**		CH_3	45	<50
27		CH_3	2	NT*	**72**		CH_3	30	50
35		CH_3	2	10	**80**		CH_3	38	13
37		CH_3	1	3	**82**		CH_3	>10	48
39		CH_3	0.8	2	**84**		CH_3	3	2
78		CH_3	23	>25	**86**		CH_3	20	50
58		CH_3	2.0	9	**94**		CH_3	0.5	0.8
30		CH_3	18	25					

*NT = not tested.

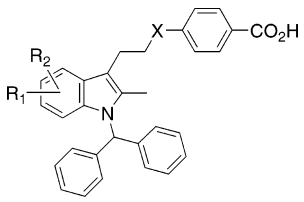
each of these compounds is a potent inhibitor of both LTB_4 and $PGF_2\alpha$ production. More importantly when exogenous arachidonic acid is added to the cells to bypass $cPLA_2\alpha$, these compounds no longer inhibit $PGF_2\alpha$ production. These leads were also examined in a human whole blood assay analogous to the rat assay, except that now inhibition of both LTB_4 and TXB_2 can be monitored. Each of these compounds equally inhibits leukotriene and thromboxane production, and the best compound, **94**, is quite potent under these conditions. It is interesting to note that each of the assays used to evaluate the compounds generates the same rank order of activity, despite the fact that they range from an isolated enzyme assay in the presence of large amounts of detergent to a human whole blood assay, where downstream products of the action of $cPLA_2\alpha$ are monitored.

Table 7 shows tabulated discovery pharmacokinetic data for these three leads. The oxygen-linked compound is a low-clearance, low-bioavailability compound, whereas the sulfone-linked compounds have much higher clearance and higher absorption. These compounds represent very well validated leads for further SAR studies.

The contributions of both the C_3 linker and the nature of the aryl acid to the inhibition of $cPLA_2\alpha$ are dramatic. In an attempt to correlate these data, a plot of GLU micelle IC_{50} vs calculated pK_a was constructed (Chart 1). The compounds encompass a fairly wide range in pK_a values from 2.3 for **157** to 4.8 for **84** and yet show no correlation to activity in the GLU micelle assay. This would indicate that the increases in potency are related to more substantial interaction with the enzyme rather than through changes in the pK_a of the benzoic acid.

One common critique of phospholipase inhibition assays is that they can be subject to numerous false positives,[101,102] due to disruption of the membrane/water interface by lipophilic compounds. It is highly unlikely that compounds **25**, **39**, and **94** are significantly disrupting the micelle in the GLU assay, since there are 350, 1325, and 2100 molecules of phospholipid or Triton for each molecule of inhibitor. Chart 2 shows a plot of $plogd_{7.4}$ (calculated) vs activity in the GLU micelle assay. It

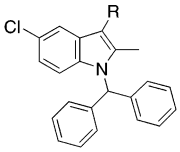
Table 4. Indole Carbocyle Variations

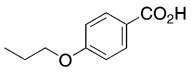
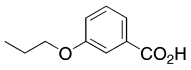
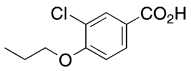
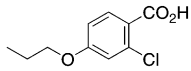
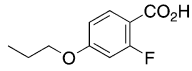
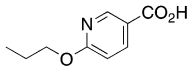
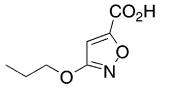


compd	R_1	R_2	X	IC50 (μM) GLU micelle	IC50 (μM) rat WB TXB_2	compd	R_1	R_2	X	IC50 (μM) GLU micelle	IC50 (μM) rat WB TXB_2
25	5-Cl	H	O	3	7	**124**	4-Cl	5-Cl	SO_2	1	4
39	5-Cl	H	SO_2	0.8	2	**126**	5-F	H	SO_2	1	5
133	6-Cl	H	O	6	13	**128**	5-OCH_3	H	SO_2	3	7
114	6-Cl	H	SO_2	4	5	**138**	5-Br	H	O	2	3
118	H	H	SO_2	2	6	**148**	5-NO_2	H	O	5	8
116	4-Cl	H	SO_2	2	12	**150**	5-NH_2	H	O	8	NA[a]
120	7-Cl	H	SO_2	6	10	**140**	5-Ph	H	O	33	9
122	5-Cl	6-Cl	SO_2	3	2	**142**	5-morph	H	O	22	>10

[a] NA = no activity at highest tested concentration (10 μM).

Table 5. Benzoate Variations



Compd	R	IC50 (μM) GLU micelle	IC50 (μM) Rat WB TXB_2
25		3	7
152		120	>50
154		11	25
88		7	25
90		2	8
155		85	NA*
157		40	>50

*NA = no activity at highest tested concentration (10 μm).

Table 6. Secondary Assays

compd	MC-9 concn (μM)	MC-9 % inhibn LTB_4	MC-9 % inhibn $PGF_2\alpha$	MC-9 % inhibn $PGF_2\alpha$ AA feed[a]	human WB IC50 (μM) TXB_2	human WB IC50 (μM) LTB_4
25	1.5	96	81	−8	34	30
39	0.5	82	72	8	8.4	6.3
94	0.5	100	100	2	1.4	0.9

[a] Exogenous arachidonic acid added to cells; see Experimental Section.

is clear from this graph that there is no correlation between the lipophilicity of the compound and the activity in the assay, For example, **39**, with a $plogd_{7.4}$ of 3.75, is among the most potent inhibitors in the series, but there are also close analogues that are quite lipophilic but are weak inhibitors, cf. **140**, $plogd_{7.4}$ of 7.33 with an IC_{50} of 33 μM.

Table 7. Pharmacokinetic Properties in the Rat

compd	CLp, mL/min/kg	%F
25	3.2	2.6
39	44	39
94	47	11

Chart 1. Plot of Activity in the GLU Micelle IC_{50} Assay vs Calculated Benzoic Acid pK_a

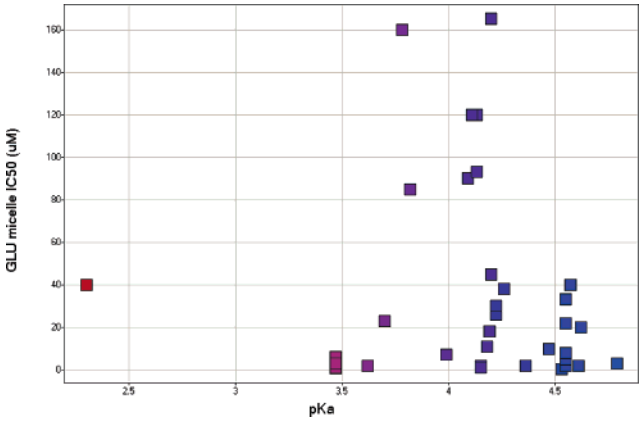


Chart 2. Graph of Calculated $plogd_{7.4}$ vs GLU Micelle IC_{50}

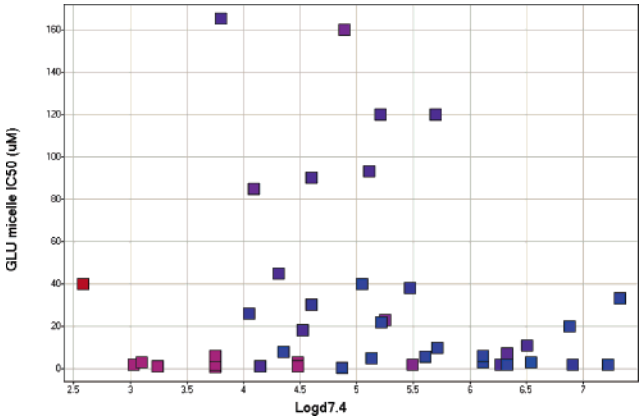
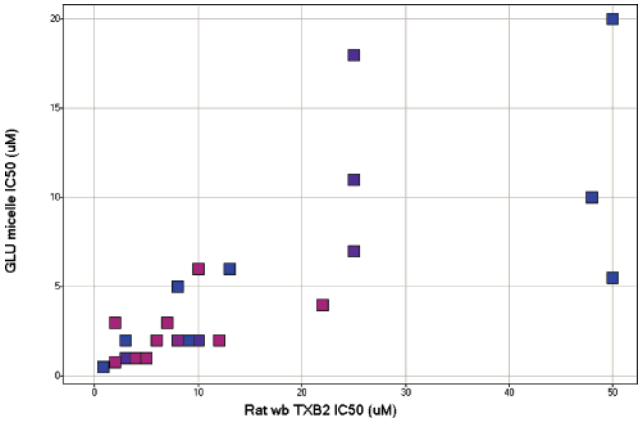


Chart 3. Graph of Rat Whole Blood IC_{50} vs GLU Micelle IC_{50}



Finally, the goal of the assay scheme is to find a primary screening assay that is predictive of activity in assays that are more physiologically relevant and eventually, after factoring in pharmacokinetics, predictive of in vivo efficacy. A graph correlating the GLU micelle IC_{50} with the rat whole blood TXB_2 IC_{50} is shown in Chart 3. These data include compounds that have an IC_{50} less than 20 μM in the GLU assay. The graph shows very clearly that not only is activity in the GLU micelle assay predictive of activity in rat whole blood, the actual IC_{50} values also correlate very well. This is probably because the GLU micelle assay, run in the presence of millimolar amounts of detergent and phospholipids, should be regarded as a very stringent primary screening assay.

Conclusions

The group of compounds described herein was very useful in defining the pharmacophore necessary for inhibition of $cPLA_2\alpha$. Starting from our initial hypothesis that a crude arachidonate mimetic was a useful starting point, our exploration began with the LTD_4 receptor antagonist zafirlukast[103] and proceeded through **1**.[81] The indole template supports a lipophilic benzhydryl group and a linker to a benzoic acid, both of which are essential parts of the pharmacophore. Optimization of the acid linker was crucial to activity and was a key step in finding compounds that were well-behaved $cPLA_2\alpha$ inhibitors. During the course of this work, the assay scheme was significantly modified until an assay more predictive of activity in physiological settings was found. The GLU micelle assay eventually filled this role; however, this was not clear until compounds with whole blood activity were found. Unfortunately, the available structure of $cPLA_2\alpha$ was not useful in predicting SAR. We believe this is primarily due to a large structural change near the active site that is postulated to occur upon membrane binding to allow the substrate access to the active site. Thus the medicinal chemistry effort was guided empirically. This paper outlines the SAR that drove this indole series of $cPLA_2\alpha$ inhibitors from a hit (**1**, $IC_{50} = 160$ μM in the GLU assay) to several viable leads (for example, **94**, $IC_{50} = 0.5$ μM in the GLU assay *and* $IC_{50} = 0.8$ μM in the rat whole blood assay). Several analogues were further proven to be selective $cPLA_2\alpha$ inhibitors using an MC-9 cell based assay, and these were also shown to have good activity against both LTB_4 and TXB_2 in human whole blood assays. Finally, discovery pharmacokinetic assays were presented to support the evaluation of these molecules as leads for further studies.

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, a 500-MHz Bruker AV-400, or a 300-MHz JEOL Eclipse spectrometer using TMS (δ 0.0) as a reference. Combustion analyses were obtained using a Perkin-Elmer series II 2400 CHNS/O analyzer or by a 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., UK) and an external Bruker APOLLO electrospray ionization (ESI) source. Flash chromatography was performed using EM Science 230−400 mesh silica gel or Biotage flash columns packed with KP−SIL 60 Å silica gel. Thin-layer chromatography (TLC) was performed using EMD 250 μm prescored silica gel 60 F_{254} plates. Purity in two solvent systems (H_2O-CH_3CN and $H_2O-MeOH$) was determined using an Agilent 1100 HPLC instrument, and all final compounds were >95% pure (see Supporting Information for details).

General Procedure for Indole Reductive Alkylation. To the indole (1.0 equiv) and the aldehyde or acetal (1.1 equiv) in CH_2Cl_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_2Cl_2, washed with H_2O 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 equiv) in DMF (0.6 M) was added to a mixture of sodium hydride (60% dispersion, 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 soln in DMF) was added. The reaction 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 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, dried, concentrated, and lyophilized to afford the carboxylic acid.

General Procedure for the Addition of Electrophiles to the Zinc Salt of an Indole.[94] The indole (1 equiv) was dissolved in anhydrous THF (0.5 M), cooled to −78 °C, and then *n*-butyllithium (1.05 equiv, 2.5 M solution in hexanes) was added over 5 min. The reaction was stirred for 30 min at −78 °C, zinc chloride (1 equiv, 1.0 M solution in THF) was added rapidly, and the reaction was allowed to warm to room temperature. Finally, the Michael acceptor or halide (1 equiv, 2 M solution in THF) was added and the reaction stirred until TLC analysis indicated that the reaction was complete. The reaction was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc, the layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl solution and brine. The organic layer was dried, evaporated, and chromatographed over silica gel.

General Procedure for Fischer Indole Synthesis. The phenylhydrazine hydrochloride (1 equiv) and the ketone (1 equiv) were placed in a biphasic mixture of CH_2Cl_2 (0.6 M) and saturated aqueous $NaHCO_3$ solution (0.6 M). The biphasic mixture was vigorously stirred for 3 h at room temperature. The organic layer was separated and the aqueous layer extracted with 20 mL of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and evaporated to a solid which was azeotroped with toluene. The

residue was then added to freshly fused and dried zinc chloride (1.2 equiv) and heated at 140 °C overnight. The reaction was cooled to room temperature and the viscous syrup partitioned between methylene chloride and H_2O. The organic layer was separated, the aqueous layer was extracted with methylene chloride, and the organic layers were combined, dried, evaporated, and purified using silica gel chromoatography.

General Procedure To Form Indole Oxoacetates. The indole (1 equiv) was dissolved in anhydrous Et_2O (0.5 M) and cooled in an ice bath. Oxalyl chloride (1 equiv) was added dropwise and the yellow suspension was stirred for 30 min with continued cooling. Then MeOH (10 equiv) was added followed by addition of NEt_3 (5 equiv). The reaction was then subjected to aqueous workup, dried, and evaporated to yield the product.

6-Chloro-1-(diphenylmethyl)-1*H*-indole (7). To a solution of 6-chloroindole (35 g, 231 mmol) in DMF (560 mL) at −5 °C was added NaH (60% dispersion in oil, 255 mmol) in one portion. The reaction mixture was stirred at −5 °C for 1 h, after which bromodiphenylmethane (57.1 g, 231 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 4 h and diluted with *tert*-butyl methyl ether, and then aqueous workup was performed. Purification by flash chromatography (100% pentane) afforded **7** (29.7 g, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, J = 3.3 Hz, 1H), 6.75 (s, 1H), 6.81 (d, J = 3.3 Hz, 1H), 7.05 − 7.1 (m, 5H), 7.21 (s, 1H), 7.32−7.39 (m, 6H), 7.55 (d, J = 7.7 Hz, 1H).

6-Chloro-1-(diphenylmethyl)-3-(oxiran-2-ylmethyl)-1*H*-indole (8). To a solution of **7** (4.2 g, 13.2 mmol) in CH_2Cl_2 (12 mL) at 0 °C were added $SnCl_4$ (1.6 mL, 13.2 mmol) and epibromohydrin (1.14 mL, 13.2 mmol). After stirring for 1 h at 0 °C, the reaction was diluted with CH_2Cl_2; washed with $NaHCO_3$, H_2O, and brine; dried; filtered; and concentrated. The crude bromohydrin was diluted with THF (60 mL), cooled to 0 °C, and treated with NaH (0.591 g, 14.7 mmol). The reaction mixture was stirred for 1 h, diluted with EtOAc, washed with H_2O and brine, dried, filtered, and concentrated. Flash chromatography (10% EtOAc/heptane) afforded **8** (2.28 g, 46%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (m, 1H), 2.78 (m, 1H), 2.96 (m, 2H), 3.14 (m, 1H), 6.73 (m, 2H), 7.04−7.09 (m, 5H), 7.20 (s, 1H), 7.30−7.35 (m, 6H), 7.55 (d, J = 9.5 Hz, 1H).

Methyl 4-[3-[6-Chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-2-hydroxypropoxy]benzoate (9). Following the procedure used to make **10**, compound **8** (1.1 g, 2.9 mmol) was converted to **9** as a colorless glass (0.55 g, 36%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (d, J = 4.5 Hz, 1H), 3.05 (dd, J = 3.4, 6.8 Hz, 2H), 3.88 (s, 3H), 3.97 (m, 2H), 4.3 (m, 2H), 6.69 (s, 2H), 6.83 (d, J = 7.2 Hz), 7.0−7.08 (m, 5H), 7.2 (s, 1H), 7.28−7.37 (m, 6H), 7.54 (d, J = 9.1 Hz, 1H), 7.98 (d, J = 7.2 Hz, 1H).

4-[3-[6-Chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-2-hydroxypropoxy]benzoic Acid (3). Compound **9** (0.095 g, 0.2 mmol) was hydrolyzed according to the general procedure to afford **3** as a white solid (0.55 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (dd, J = 15.4, 2.3 Hz, 2H), 3.98 (m, 2H), 4.29 (m, 1H), 6.71 (s, 2H), 6.94 (d, J = 8.6 Hz, 1H), 7.05−7.12 (m, 5H), 7.22 (s, 1H), 7.29−7.38 (m, 6H), 7.55 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.6 Hz, 2H).

Methyl 3-[3-[6-Chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-2-hydroxypropoxy]benzoate (10). To a solution of **8** (1.1 g, 2.9 mmol) in DMF (10 mL) was added methyl 3-hydroxybenzoate (0.45 g, 2.9 mmol) followed by KO-*t*Bu (0.033 g, 0.29 mmol). The reaction was stirred for 20 h. Another portion of KO-*t*Bu (0.033 g, 0.29 mmol) was added, and the mixture was heated to 80 °C for 4 h; diluted with EtOAc; washed with saturated $NaHCO_3$, H_2O, and brine; dried; filtered; and concentrated. Flash chromatography (10% EtOAc/heptane) afforded **10** (0.53 g, 34%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (br s, 1H), 3.06 (m, 2H), 3.91 (s, 3H), 3.98 (m, 2H), 4.27 (m, 1H), 6.71 (s, 2H), 7.01−7.13 (m, 6H), 7.22 (s, 1H), 7.29−7.42 (m, 6H), 7.55 (m, 2H), 7.73 (d, J = 8.6 Hz, 1H).

3-[3-[6-Chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-2-hydroxypropoxy]benzoic Acid (4). Compound **10** (0.1 g, 0.19 mmol) was hydrolyzed according to the general procedure to afford **4** as a pale yellow glass (0.9 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (dd, J = 7.7, 1.7 Hz, 2H), 3.97 (m, 2H), 4.3 (m, 1H), 6.72 (s, 2H), 7.03−7.15 (m, 7H), 7.22 (s, 1H), 7.28−7.3 (m, 9H), 7.58 (m, 2H), 7.75 (d, J = 8.5 Hz, 2H).

Methyl 4-(2,2-Diethoxyethoxy)benzoate (14). To methyl 4-hydroxybenzoate (1.0 equiv) in DMF (0.83 M) was added K_2CO_3 (2.0 equiv) followed by 2-bromo-1,1-diethoxyethane (1.0 equiv) and the reaction mixture was stirred at 110 °C for 2 d. The reaction mixture was diluted with EtOAc; washed with 1 N NaOH, H_2O, and brine; dried over Na_2SO_4; and concentrated to afford **14** in 84% yield. This material was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 9.3 Hz, 6H), 3.62 (m, 2H), 3.73 (m, 2H), 3.86 (s, 3H), 4.03 (d, J = 5.1 Hz, 2H), 4.82 (t, J = 5.4 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 8.9 Hz, 2H).

Methyl 4-(2-Oxoethoxy)benzoate (18). To **14** (1.0 equiv) in $CHCl_3$ (0.32 M) was added H_2O (2.0 equiv) followed by the dropwise addition of TFA (2.0 equiv). The reaction mixture was stirred at room temperature overnight, diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to yield **18** in 80% yield.

Methyl 4-[2-(5-Chloro-2-methyl-1*H*-indol-3-yl)ethoxy]benzoate (21). 5-Chloro-2-methyl-1*H*-indole and **18** were condensed using the general reductive alkylation procedure to yield 92% of **21** after purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.16 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 4.16 (t, J = 7.1 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.09 (m, 1H), 7.17 (m, 1H), 7.51 (s, 1H), 7.82 (br s, 1H), 7.95 (d, J = 9.1 Hz, 2H).

Methyl 4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoate (24). Compound **21** was N-alkylated as described in the general procedure to yield **24** in 72% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.19 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 4.16 (t, J = 7.2 Hz, 2H), 5.85 (s, 1H), 6.54 (d, J = 9.0 Hz, 1H), 6.85 (m, 3H), 7.11 (m, 4H), 7.31(m, 6H), 7.51 (d, J = 2.2 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H).

4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (25). Compound **24** was hydrolyzed according to the general procedure to yield **25** in 80% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.36 (s, 3H), 3.24 (t, J = 6.7 Hz, 2H), 4.27 (t, J = 6.6 Hz, 2H), 6.68 (d, J = 8.00 Hz, 1H), 6.79 (dd, J = 8.8, 2.2 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 7.13 (m, 5H), 7.35 (m, 6H), 7.62 (d, J = 2.2 Hz, 1H), 7.93 (d, J = 8.8 Hz, 2H). Anal. ($C_{31}H_{26}ClNO_3$): C, H, N.

Methyl 4-[3-(5-Chloro-2-methyl-1*H*-indol-3-yl)propyl]benzoate (22). 5-Chloro-2-methyl-1*H*-indole and methyl 4-(3-oxopropyl)benzoate[104] were condensed using the general reductive alkylation procedure to yield 90% of **22** after purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87−2.04 (m, 2 H), 2.33 (s, 3 H), 2.62−2.78 (m, 4 H), 3.91 (s, 3 H), 7.03−7.08 (m, 1 H), 7.16−7.20 (m, 1 H), 7.24 (s, 1 H), 7.25−7.28 (m, 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 (26). Compound **22** was N-alkylated as described in the general procedure to yield **26** in 75% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84−1.99 (m, 2 H) 2.15 (s, 3 H) 2.61−2.74 (m, 4 H) 3.87 (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) 7.17−7.24 (m, 3 H) 7.26−7.31 (m, 5 H) 7.38 (d, J = 1.9 Hz, 1 H) 7.91 (d, J = 8.2 Hz, 2 H).

4-[3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-propyl]benzoic Acid (27). Compound **26** was hydrolyzed as per the general procedure to afford **27** in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 1 H), 1.87−2.01 (m, 2 H), 2.16 (s, 3 H), 2.63−2.74 (m, 4 H), 6.49 (d, J = 8.79 Hz, 1 H), 6.76 (dd, J = 8.79, 1.92 Hz, 1 H), 6.83 (s, 1 H), 7.03−7.10 (m, 4 H), 7.25 (m, 8 H), 7.40 (d, J = 1.92 Hz, 1 H), 7.99 (d, J = 7.97 Hz, 2 H).

4-[(2,2-Diethoxyethyl)thio]benzoic Acid (15). To 4-mercaptobenzoic acid (1.0 equiv) in DMF (0.32 M) was added K_2CO_3 (2.0 equiv) followed by 2-bromo-1,1-diethoxyethane (1.0 equiv). After 18 h the reaction mixture was diluted with EtOAc and washed with H_2O and brine, and then the organic layer was concentrated.

Trituration with 20% EtOAc in hexanes gave **15** in 81% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.4 Hz, 6H), 3.22 (d, J = 5.5 Hz, 2H), 3.69 (m, 2H), 3.73 (m, 2H), 4.87 (t, J = 5.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H).

Methyl 4-[(2,2-Diethoxyethyl)thio]benzoate (16). To **15** (1.0 equiv) in CH_2Cl_2 (0.24 M) was added DMF followed by oxalyl chloride (1.1 equiv). After stirring for 2 h at 25 °C, Et_3N (2.0 equiv) and MeOH (3.0 equiv) were added, stirring was continued overnight, and then the solvent was evaporated to yield **16** in 96% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (t, J = 7.2 Hz, 6H), 3.24 (d, J = 5.5 Hz, 2H), 3.50 (m, 2H), 3.62 (m, 2H), 3.84 (s, 3H), 4.67 (t, J = 5.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H).

Methyl 4-[(2-Oxoethyl)thio]benzoate (19). Compound **16** (1.0 equiv) was dissolved in $CHCl_3$ (0.32 M), and H_2O (2.0 equiv) was added followed by the dropwise addition of TFA (2.0 equiv). The reaction mixture was stirred at room temperature overnight, diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to afford **19** in 73% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (d, J = 3.0 Hz, 2H), 3.84 (s, 3H), 7.27 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 9.59 (t, J = 3.0 Hz, 1H).

5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indole (33). 5-Chloro-2-methyl-1*H*-indole was alkylated with bromodiphenylmethane as in the general procedure to yield 25% of **33** contaminated with 5-chloro-1,3-bis(diphenylmethyl)-2-methyl-1*H*-indole resulting from the addition of a second benzhydryl to the C_3 position. All additional reactions were performed with this material.

Methyl 4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]thio]benzoate (34). Compound **33** and **19** were condensed as in the general procedure to yield 25% of **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.06 (t, J = 7.4 Hz, 2H), 3.24 (t, J = 7.6 Hz, 2H), 3.90 (s, 3H), 6.53 (d, J = 8.8 Hz, 1H), 6.84 (m, 2H), 7.08 (m, 4H), 7.26 (m, 8H), 7.32 (d, J = 3.3 Hz, 1H), 7.91 (d, J = 8.5 Hz, 2H).

4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]thio]benzoic Acid (35). Compound **34** was hydrolyzed according to the general procedure to afford **35** in 78% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.36 (s, 3H), 3.19 (t, J = 6.8 Hz, 2H), 3.43 (t, J = 7.2 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.84 (m, 1H), 7.19 (m, 5H), 7.42 (m, 8H), 7.62 (s, 1H), 7.97 (d, J = 8.5 Hz, 2H). Anal. ($C_{31}H_{26}ClNO_2S\cdot 0.3C_6H_{14}$): C, H, N.

Methyl 4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfinyl]benzoate (36) and Methyl 4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (38). Compound **34** (1.0 equiv) was dissolved in acetone, methanol, and H_2O (0.3 M) and treated with Oxone (1.0 equiv). After being stirred for 1 d at 25 °C, the reaction mixture was diluted with $CHCl_3$, washed with H_2O and brine, dried over Na_2SO_4, and purified to give both sulfoxide **36** (29%) and the sulfone **38** (36%). **36**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.96 (m, 2H), 3.08 (m, 2H), 3.95 (s, 3H), 6.52 (d, J = 8.8 Hz, 1H), 6.78 (m, 2H), 7.05 (m, 4H), 7.29 (m, 8H), 7.71 (d, J = 3.4 Hz, 1H), 8.19 (d, J = 8.5 Hz, 2H). **38**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.17 (m, 2H), 3.32 (m, 2H), 3.98 (s, 3H), 6.50 (d, J = 9.0 Hz, 1H), 6.80 (m, 2H), 7.05 (m, 4H), 7.30 (m, 7H), 8.03 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 8.5 Hz, 2H).

4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]sulfinyl]benzoic Acid (37). Compound **36** was hydrolyzed according to the general procedure to afford **37** in 80% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.30 (s, 3H), 3.00 (m, 2H), 3.26 (m, 2H), 3.95 (s, 3H), 6.66 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 1.9, 8.8 Hz, 1H), 7.11 (m, 5H), 7.35 (m, 7H), 7.83 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H). Anal. ($C_{31}H_{26}ClNO_3S$): C, H, N.

4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]sulfonyl]benzoic Acid (39). Compound **38** was hydrolyzed according to the general procedure to afford **39** in 79% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.26 (s, 3H), 3.14 (m, 2H), 3.56 (m, 2H), 6.63 (d, J = 8.5 Hz, 1H), 6.75 (dd, J = 1.9, 8.8 Hz, 1H), 7.09 (m, 5H), 7.26 (d, J = 2.2 Hz, 1H), 7.34 (m, 6H), 8.10 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H). Anal. ($C_{31}H_{26}ClNO_4S$): C, H, N.

Methyl 4-[2-[(2,2-Diethoxyethyl)thio]ethyl]benzoate (17). Compound **13**[105] was dissolved in THF (0.2 M) and treated with NaH (1.1 equiv of a 60% oil dispersion), 2-bromo-1,1-diethoxyethane (1.1 equiv) was added, and the reaction was heated at 55 °C for 2 h. Workup and chromatography yielded the desired product **17** in 86% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J = 6.8 Hz, 6H), 2.71 (d, J = 5.5 Hz, 2H), 2.90 (m, 4H), 3.54 (m, 2H), 3.67 (m, 2H), 3.91 (s, 3H), 4.60 (t, J = 5.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2 H), 7.97 (d, J = 8.2 Hz, 2H).

Methyl 4-[2-[(2-Oxoethyl)thio]ethyl]benzoate (20). Compound **17** was dissolved in $CHCl_3$:TFA: H_2O (2:1:1, 0.2 M final concentration) and stirred for 1.5 h. Workup yielded the desired aldehyde **20** in a quantitative crude yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 3.19 (d, J = 3.6 Hz, 2H), 3.91 (s, 3H), 7.26 (d, J = 8.0 Hz, 2 H), 7.98 (d, J = 8.3 Hz, 2H), 9.47 (d, J = 3.6 Hz, 2H).

Methyl 4-[2-[[2-(5-Chloro-2-methyl-1*H*-indol-3-yl)ethyl]thio]-ethyl]benzoate (23). 5-Chloro-2-methyl-1*H*-indol and **20** were condensed as in the general reductive alkylation procedure to yield 66% of **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.77 (m, 4H), 2.92 (m, 4H), 3.90 (s, 3H), 7.18 (m, 4H), 7.26 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.5 Hz, 2H).

Methyl 4-[2-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]thio]ethyl]benzoate (28). Compound **23** was alkylated with bromodiphenylmethane as in the general procedure to yield 57% of **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.81 (m, 8H), 3.90 (s, 3H), 6.53 (d, J = 8.8 Hz, 1H), 6.84 (m, 3H), 7.11 (m, 5H), 7.28 (m, 6H), 7.38 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H).

Methyl 4-[2-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfinyl]ethyl]benzoate (29). Compound **28** was stirred in acetone, H_2O, and aqueous H_2O_2 (35 wt %, 100 equiv) for 2 h at room temperature. Workup and chromatography yielded **29** in 66% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.00 (m, 8H), 3.91 (s, 3H), 6.56 (d, J = 8.6 Hz, 1H), 6.85 (m, 3H), 7.08 (m, 5H), 7.29 (m, 6H), 7.41 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H).

4-[2-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfinyl]ethyl]benzoic Acid (30). Compound **29** was hydrolyzed according to the general procedure to yield **30** in 35% yield: ^{1}H NMR (400 MHz, CD_3OD) δ 2.56 (s, 3H) 3.34 (m, 4H) 3.46 (m, 3H) 3.86 (m, 1H) 6.86 (d, J = 8.8 Hz, 1H) 7.04 (m, 1H) 7.36 (s, 4H) 7.46 (m, 3H) 7.59 (m, 6H) 7.83 (d, J = 1.7 Hz, 1H) 8.16 (d, J = 7.8 Hz, 2H). Anal. ($C_{33}H_{30}ClNO_3S$): C, H, N.

Methyl 4-[2-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]ethyl]benzoate (31). Compound **28** was dissolved in CH_3CN (0.03 M), treated with NMO (3 equiv), TPAP (0.1 equiv), and molecular sieves, and stirred at room temperature for 2 h. Workup yielded 49% of the title compound **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.90 (m, 2H), 2.98 (m, 2H), 3.30 (s, 4H) 3.91 (s, 3H), 6.58 (d, J = 9.1 Hz, 1H), 6.82 (s, 1H), 6.91 (m, 3H), 6.99 (d, J = 7.2 Hz, 2 H), 7.23 (m, 8H), 7.47 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H).

4-[2-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]ethyl]benzoic Acid (32). Compound **31** was hydrolyzed according to the general procedure to yield **32** in 76% yield: ^{1}H NMR (400 MHz, CD_3OD) δ 2.59 (m, 3 H), 3.21 (s, 4 H), 3.61 (m, 2 H), 3.69 (m, 2 H), 6.93 (d, J = 9.1 Hz, 1H), 7.15 (m, 3H), 7.31 (m, 5H), 7.56 (m, 6H), 7.93 (d, J = 1.8 Hz, 1H), 8.13 (d, J = 8.3 Hz, 2H). Anal. ($C_{33}H_{30}ClNO_4S$): C, H, N.

Methyl 4-[2-(5-Chloro-1*H*-indol-3-yl)ethoxy]benzoate (41). To a solution of the indole alcohol **40**[93] (1 g, 5.1 mmol) in CH_2Cl_2 at 0 °C was added NEt_3 (0.86 mL, 6.1 mmol) followed by MsCl (0.415 mL, 5.4 mmol). The reaction was stirred for 20 min, subjected to an aqueous workup, and concentrated. The residue was azeotroped with benzene and used in the next step without further purification. To a solution of methyl 4-hydroxybenzoate (1 g, 6.5 mmol) in DMF (20 mL) at 0 °C was added NaH (0.25 g, 6.5 mmol, 60% oil dispersion). The reaction was removed from the ice bath and stirred for 20 min, and then a solution of the indole mesylate (~5.1 mmol)

was added in DMF (5 mL). The reaction was stirred at 40 °C overnight, diluted with EtOAc, washed with brine, dried, filtered, and concentrated. Flash chromatograpghy (20% EtOAc/hexanes) afforded **41** (0.62 g, 37% over two steps): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.15 (t, J = 6.7 Hz, 2H), 3.80 (s, 3H), 4.28 (t, J = 6.8 Hz, 2H), 7.03−7.11 (m, 3H), 7.34 (d, J = 2.3 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 9.1 Hz, 2H).

Methyl 4-[2-[5-Chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-ethoxy]benzoate (42): Compound **41** was N-alkylated according to the general procedure to afford **42** as a colorless oil in 60% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (t, J = 6.9 Hz, 2H), 3.88 (s, 3 H), 4.19 (t, J = 6.9 Hz, 2H), 6.72−6.76 (m, 2 H), 6.83 (d, J = 8.8 Hz, 2H), 7.02−7.15 (m, 6H), 7.29−7.41 (m, 6H), 7.62 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H).

4-[2-[5-Chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy]benzoic Acid (43). Compound **42** was hydrolyzed according to the general procedure to yield **43** in 79% yield: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.13 (t, J = 6.7 Hz, 2H), 4.23 (t, J = 6.6 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 7.03 (s, 1 H), 7.06−7.15 (m, 6H), 7.28−7.40 (m, 6H), 7.43 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H).

2-*tert*-Butyl-5-chloro-1*H*-indole[106] **(44).** 4-Chlorophenylhydrazine hydrochloride and 3,3-dimethylbutan-2-one were reacted following the Fischer indole general procedure to give **44** in 50% yield after purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H), 6.09 (s, 1H), 6.95 (dd, J = 8.7, 1.8 Hz, 1H), 7.13 (m, 1H), 7.38 (s, 1H), 7.92 (br. s, 1H).

Methyl (2-*tert*-Butyl-5-chloro-1*H*-indol-3-yl)oxoacetate (46). Following the general procedure to form indole oxoacetates, indole **44** was treated with oxalyl chloride and then quenched with MeOH to afford **46** in 50% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 3.89 (s, 3H), 7.04 (dd, J = 8.5, 1.8 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 9.18 (br s, 1H).

2-(2-*tert*-Butyl-5-chloro-1*H*-indol-3-yl)ethanol (47). Compound **46** was reduced with $LiAlH_4$ following the procedure for **130** to give **47** in 76% yield: ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 3.01 (t, J = 7.1 Hz, 2H), 3.75 (t, J = 7.1 Hz, 2H), 6.95 (dd, J = 8.5, 2.0 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.86 (br s, 1H).

2-[2-*tert*-Butyl-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-ethanol (50). Compound **49** was N-alkylated as described in the general procedure to give **50** in 31% yield: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.18 (t, J = 7.3 Hz, 2H), 3.76 (t, J = 7.4 Hz, 2H), 6.34 (d, J = 8.9 Hz, 1H), 6.58 (dd, J = 2.2, 8.9 Hz, 1H), 6.90 (m, 5H), 7.19 (m, 6H), 7.39 (d, J = 2.06 Hz, 2H).

Methyl 4-[2-[2-*tert*-Butyl-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy]benzoate (52). Following the Mitsunobu procedure used to make **132**, reaction of methyl 4-hydroxybenzoate and **50** afforded **52** in 30% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 3.42 (t, J = 7.7 Hz, 2H), 3.76 (s, 3H), 4.11 (t, J = 7.4 Hz, 2H), 6.35 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 8.8, 1.9 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.98 (m, 5H), 7.18 (m, 6H), 7.38 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 8.9 Hz, 2H).

4-[2-[2-*tert*-Butyl-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]-ethoxy]benzoic Acid (53). Compound **52** was hydrolyzed according to the general procedure to afford 52 in 94% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (s, 9H), 3.30 (t, J = 7.1 Hz, 2H), 4.12 (t, J = 7.0 Hz, 2H), 6.26 (d, J = 8.8 Hz, 1H), 6.58 (m, 1H), 6.89 (m, 5H), 7.20 (m, 8H), 7.47 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H).

5-Chloro-2-phenyl-1*H*-indole[107] **(45).** 4-Chlorophenylhydrazine hydrochloride and 1-phenylethanone were treated as in the Fischer indole general procedure to yield **45** in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (s, 1H), 7.02 (dd, J = 8.6, 1.9 Hz, 1H), 7.19 (m, 3H), 7.33 (t, J = 7.14, 1.9 Hz, 1H), 7.50 (m, 3H), 8.27 (br s, 1H).

Methyl (5-Chloro-2-phenyl-1*H*-indol-3-yl)oxoacetate (48). Following the general procedure to functionalize at C_3 with oxalyl chloride, **45** yielded **48** in 80% crude yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 7.17 (m, 4H), 7.32 (m, 2H), 7.51 (d, J = 7.5 Hz, 1H), 8.25 (d, J = 1.9 Hz, 1H), 8.38 (br s, 1H).

2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)ethanol (49). Compound **48** was reduced using the procedure for **130** to yield **49** in 80% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (t, J = 6.6 Hz, 2H), 3.83 (q, J = 6.5 Hz, 2H), 7.05 (dd, J = 8.5, 1.9 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.33 (m, 3H), 7.50 (m, 3H), 7.19 (br s, 1H).

2-[5-Chloro-1-(diphenylmethyl)-2-phenyl-1*H*-indol-3-yl]ethanol (51). Compound **49** was N-alkylated as described in the general procedure to yield **51** in 40% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (t, J = 6.6 Hz, 2H), 3.67 (m, 2H), 6.46 (s, 1H), 6.56 (d, J = 8.8 Hz, 1H), 6.75 (dd, J = 2.1 Hz, 8.9, 1H), 6.92 (m, 4H), 7.14 (m, 7H), 7.29 (m, 3H), 7.48 (d, J = 2.1 Hz, 2H).

Methyl 4-[2-[5-Chloro-1-(diphenylmethyl)-2-phenyl-1*H*-indol-3-yl]ethoxy]benzoate (54). Applying the Mitsunobu procedure used to make **132**, reaction of methyl 4-hydroxybenzoate and **51** afforded **54** in 67% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (t, J = 7.1 Hz, 2H), 3.75 (s, 3H), 4.07 (t, J = 7.2 Hz, 2H), 6.46 (s, 1H), 6.55 (d, J = 8.8 Hz, 1H), 6.54 (d, J = 8.9 Hz, 2H), 6.75 (dd, J = 8.9, 2.2 Hz, 1H), 7.15 (m, 7H), 7.30 (m, 4H), 7.52 (d, J = 2.1 Hz, 2H), 7.79 (d, J = 8.9 Hz, 2H).

4-[2-[5-Chloro-1-(diphenylmethyl)-2-phenyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (55). Compound **54** was hydrolyzed according to the general procedure to afford **55** in 89% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.89 (t, J = 6.9 Hz, 2H), 4.04 (t, J = 7.0 Hz, 2H), 6.45 (s, 1H), 6.53 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.9, 2.2 Hz, 1H), 6.86 (m, 4H), 7.20 (m, 7H), 7.35 (m, 2H), 7.66 (m, 2H).

Methyl 4-[4-(5-Chloro-2-methyl-1*H*-indol-3-yl)butoxy]benzoate (56). 5-Chloro-2-methyl-1*H*-indole and methyl 4-(4-bromobutoxy)benzoate[108] were treated under the general Zn salt alkylation conditions to yield **56** in 23% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−1.92 (m, 4H), 2.39 (s, 3H), 2.75 (t, J = 6.9 Hz, 2H), 3.91 (s, 3H), 4.03 (t, J = 6.1 Hz, 2H), 6.91 (d, J = 9.1 Hz, 1H), 7.07 (dd, J = 9.1, 1.8 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 1.7 Hz, 1H), 7.82 (s, 1 H), 8.00 (d, J = 8.8 Hz, 2H).

Methyl 4-[4-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]butoxy]benzoate (57). Compound **56** was N-alkylated according to the general procedure to afford **57** in 29% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77−1.95 (m, 4H), 2.30 (s, 3H), 2.80 (t, J = 6.7 Hz, 2H), 3.92 (s, 3H), 4.04 (t, J = 5.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 1H), 6.83 (dd, J = 8.8, 2.2 Hz, 1H), 6.89−6.96 (m, 3H), 7.10−7.17 (m, 4H), 7.31−7.46 (m, 6H), 7.51 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 9.1 Hz, 2H).

4-[4-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-butoxy]benzoic Acid (58). Compound **57** was hydrolyzed according to the general procedure to afford **58** in 46% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−1.94 (m, 4H), 2.29 (s, 3H), 2.79 (t, J = 7.0 Hz, 2H), 4.06 (t, J = 5.9 Hz, 2H), 6.55 (d, J = 8.8 Hz, 1H), 6.82 (dd, J = 8.8, 2.2 Hz, 1H), 6.89 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.09−7.16 (m, 4H), 7.30−7.45 (m, 6H), 7.50 (d, J = 1.9 Hz, 1H), 8.07 (d, J = 8.8 Hz, 2H).

Methyl (5-Chloro-2-methyl-1*H*-indol-3-yl)acetate (59). 5-Chloro-2-methyl-1*H*-indole and methyl bromoacetate were treated under the general Zn salt alkylation conditions to yield **59** in 47% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 2.39 (s, 3H), 3.68 (m, 3H), 4.93 (s, 2H), 6.99 (dd, J = 8.5, 1.9 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 1.9 Hz, 1H).

Methyl [5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]acetate (60). Compound **59** was N-alkylated according to the general procedure to afford the title compound in 77% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 2.28 (s, 3H), 3.72 (s, 3H), 4.93 (s, 2H), 6.57 (d, J = 9.1 Hz, 1H), 6.74 (dd, J = 8.8, 2.2 Hz, 1H), 7.04 (s, 1H), 7.08−7.14 (m, J = 6.7, 2.9 Hz, 4H), 7.28−7.34 (m, 6H), 7.46 (d, J = 2.2 Hz, 1H).

[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]acetic Acid (61). Compound **60** was hydrolyzed according to the general procedure to afford **61** in 86% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 2.29 (s, 3H), 3.39 (m, 2H), 6.57 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.8, 2.2 Hz, 1H), 7.05 (s, 1H), 7.09−7.16 (m, 4H), 7.30−7.35 (m, J = 4.3, 2.3 Hz, 6H), 7.48 (d, J = 1.9 Hz, 1H).

Methyl 4-[[[[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]acetyl]amino]methyl]benzoate (62). Compound **61** (1 equiv) was dissolved in DMF (0.1 M); subsequently treated with EDCI (1.2 equiv), DMAP (1.2 equiv), and methyl 4-(aminomethyl)-benzoate (2.0 equiv); and then stirred overnight. Workup and purification yielded 73% of **62**: ^{1}H NMR (300 MHz, CD_3OD) δ 2.29 (s, 3H), 3.69 (s, 2H), 3.89 (s, 3H), 4.43 (s, 2H), 6.59 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.9, 2.1 Hz, 1H), 7.07 (s, 1H), 7.10−7.16 (m, J = 6.6, 3.0 Hz, 4H), 7.26−7.36 (m, 8H), 7.53 (d, J = 2.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H).

4-[[[[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-acetyl]amino]methyl]benzoic Acid (63). Compound **62** was hydrolyzed according to the general procedure to afford **63** in 59% yield: ^{1}H NMR (300 MHz, CD_3OD) δ 2.32 (s, 3H), 3.70 (s, 2H), 4.44 (s, 2H), 6.60 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8, 2.2 Hz, 1H), 7.08 (s, 1H), 7.11−7.17 (m, J = 6.7, 2.3 Hz, 4H), 7.27−7.37 (m, 8H), 7.54 (d, J = 1.9 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H).

Ethyl 4-[[[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]oxoacetyl]amino]benzoate (64). Compound **33** was treated with oxalyl chloride as described in the general procedure for the preparation of indole oxoacetates. The resulting intermediate was reacted with ethyl 4-aminobenzoate (5 equiv) and then allowed to stir at room temperature overnight. Workup and chromatography yielded 46% of the desired **64**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 2.70 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 6.65 (d, J = 8.8 Hz, 1H), 6.92 (dd, J = 8.8, 1.95 Hz, 1H), 7.02 (s, 1H), 7.15 (m, 4H), 7.36 (m, 6H), 7.91 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 1.9 Hz, 1H).

4-[[[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-oxoacetyl]amino]benzoic Acid (65). Compound **64** was hydrolyzed in 85% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 3 H), 6.66 (m, 1 H), 6.92 (m, 1 H), 7.02 (s, 1 H), 7.15 (m, 4 H), 7.36 (m, 6 H), 7.50 (d, J = 8.5 Hz, 2 H), 8.16 (m, 3 H). Anal. ($C_{31}H_{26}ClNO_2S\cdot 0.4H_2O$): C, H, N.

Ethyl 3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]propanoate (67). Compound **66**[109] was N-alkylated according to the general procedure which afforded **67** in 37% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 2.58 (t, J = 7.4 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 2.2, 8.8 Hz, 1H), 6.85 (s, 1H), 7.08 (m, 4H), 7.32 (m, 6H), 7.46 (d, J = 1.9 Hz, 1H).

3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]propanoic Acid (68). Compound **67** was hydrolyzed using the standard conditions to afford **68** in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.64 (t, J = 7.5 Hz, 2H), 3.03 (t, J = 7.4 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 1.9, 8.8 Hz, 1H), 6.85 (s, 1H), 7.08 (m, 4H), 7.32 (m, 6H), 7.45 (d, J = 2.2 Hz, 1H).

Methyl 4-[[[3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]propanoyl]amino]methyl]benzoate (69). Compound **68** (1.0 equiv) was dissolved in CH_2Cl_2 (0.04 M) and treated with EDCI (1.3 equiv), DMAP (0.1 equiv), DIEA (1.5 equiv), and methyl 4-(aminomethyl)benzoate (1.1 equiv). The reaction was stirred for 18 h, and aqueous workup and chromatography yielded 72% of **69**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.53 (t, J = 7.4 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 3.90 (s, 3H), 4.32 (d, J = 5.8 Hz, 2H), 5.52 (br s, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 2.2, 8.8 Hz, 1H), 6.82 (s, 1H), 7.07 (m, 4H), 7.13 (d, J = 8.2 Hz, 2H), 7.29 (m, 6H), 7.46 (d, J = 2.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H).

4-[[[3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-propanoyl]methylamino]methyl]benzoic Acid (70). Compound **69** was hydrolyzed according to the general procedure to afford **70** in 92% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.40 (t, J = 7.4 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 4.27 (d, J = 6.0 Hz, 2H), 6.64 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 1.9, 8.8 Hz, 1H), 7.06 (m, 4H), 7.14 (s, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.34 (m, 6H), 7.53 (d, J = 1.9 Hz, 1H) 7.79 (d, J = 8.3 Hz, 2H), 8.36 (t, J = 5.8 Hz, 1H). Anal. ($C_{33}H_{29}ClN_2O_3$): C, H, N.

Methyl 4-[[[3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]propanoyl]methylamino]methyl]benzoate (71). Compound **69** was dissolved in DMF (0.02 M) and treated with NaH (60% dispersion, 2 equiv) followed by MeI (6 equiv). Stirring at room temperature overnight followed by workup and chromatography gave **71** in 59% yield (two rotamers present; data for major one shown): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 2.67 (t, J = 7.2 Hz, 2H), 2.75 (s, 3H), 3.10 (m, 2H), 3.91 (s, 3H), 4.58 (s, 2H), 6.53 (d, J = 9.1 Hz, 1H), 6.80 (dd, J = 1.9, 8.8 Hz, 1H), 6.84 (s, 1H), 7.07 (m, 5H), 7.31 (m, 7H), 7.48 (d, J = 1.9 Hz, 1H), 7.94 (m, 2H).

4-[[[3-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-propanoyl]amino]methyl]benzoic Acid (72). Compound **71** was hydrolyzed according to the general procedure to afford **72** in 72% yield (two rotamers present; data for major one shown): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.63 (t, J = 6.9 Hz, 2H), 2.76 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H), 4.51 (s, 2H), 6.65 (d, J = 8.8 Hz, 1H), 6.81 (dd, J = 2.0, 8.5 Hz, 1H), 7.07 (m, 4H), 7.15 (s, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.33 (m, 6H), 7.54 (d, J = 2.2 Hz, 1H) 7.83 (d, J = 8.0 Hz, 2H).

Ethyl (5-Chloro-2-methyl-1*H*-indol-3-yl)acetate (73). 4-Chlorophenylhydrazine hydrochloride and ethyl levulinate were treated as in the Fischer indole general procedure to afford **73** in 26% yield after purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3H), 2.21 (s, 3H), 3.49 (s, 2H), 4.00 (q, J = 7.1 Hz, 2H), 6.90 (dd, J = 8.2,1.9 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.92 (br s, 1H).

Ethyl [5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-acetate (74). Compound **73** was alkylated with bromodiphenylmethane as described in the general procedure to afford **74** in 17% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3H), 2.17 (s, 3H), 3.52 (s, 2H), 4.00 (q, J = 7.1 Hz, 2H), 6.41 (d, J = 8.8 Hz, 1H), 6.67 (dd, J = 8.9, 2.1 Hz, 1H), 6.75 (s, 1H), 6.98 (m, 4H), 7.16 (m, 5H), 7.37 (m, 2H).

2-(1-Benzhydryl-5-chloro-2-methyl-1*H*-indol-3-yl)ethanol (75). Compound **74** was reduced using the procedure for **130** to give **75** in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.84 (t, J = 6.5 Hz, 2H), 3.69 (q, J = 6.4 Hz, 3H), 6.41 (d, J = 8.9 Hz, 1H), 6.68 (dd, J = 8.8, 2.1 Hz, 1H), 6.75 (s, 1H), 7.00 (m, 4H), 7.19 (m, 5H), 7.36 (d, J = 1.9 Hz, 1H).

[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]acetaldehyde (76). Compound **75** was dissolved in CH_2Cl_2 (0.02 M), treated with the Dess−Martin periodinane[110] (1.2 equiv), and stirred for 40 min, and workup and chromatography yielded 92% of **76**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.72 (d, J = 2.7 Hz, 2H), 6.56 (d, J = 8.8 Hz, 1H), 6.84 (dd, J = 8.8, 2.2 Hz, 1H), 6.89 (s, 1H), 7.10 (m, 4H), 7.32 (m, 6H), 7.43 (d, J = 1.9 Hz, 1H), 9.64 (d, J = 2.8 Hz, 1H).

Methyl 4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]amino]benzoate (77). Compound **76** was dissolved in MeOH (0.09 M) and treated with methyl 4-aminobenzoate (1.1 equiv) and AcOH (3.5 equiv) followed by $NaBH_3CN$ (1.2 equiv).[97] Workup and purification yielded the title compound **77** in 88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.00 (t, J = 6.9 Hz, 2H), 3.45 (q, J = 6.4 Hz, 2H), 3.84 (s, 3H), 4.11 (br s, 1H), 6.47 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.8 Hz, 1H), 6.81 (m, 2H), 7.08 (m, 4H), 7.32 (m, 6H), 7.45 (d, J = 2.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H).

4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]amino]benzoic Acid (78). Compound **77** was hydrolyzed according to the general procedure to afford **78** in 90% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.01 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 6.45 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.84 (m, 2H), 7.08 (m, 4H), 7.32 (m, 6H), 7.87 (d, J = 8.6 Hz, 2H).

Ethyl 4-[[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]carbonyl]amino]benzoate (79). Compound **75** was treated with ethyl 4-isocyanatobenzoate (1.5 equiv) in THF (0.5 M) and stirred for 1 h. Workup and chromatography yielded the title compound **79** in 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H), 4.34 (q, J = 6.3 Hz, 2H), 6.61 (m, 2H), 6.86 (m, 2H), 7.07 (m, 4H), 7.29 (m, 7H), 7.51 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H).

4-[[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]carbonyl]amino]benzoic Acid (80). Compound **79** was hydrolyzed according to the general procedure to afford **80** in 76% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.32 (s, 3H), 3.12 (m, 2H), 4.33 (m, 2H), 6.58 (d, J = 8.9 Hz, 1H), 6.75 (dd, J = 8.9, 2.1 Hz, 1H), 7.05 (s, 1H), 7.15 (m, 3H), 7.32 (m, 5H), 7.41 (m, 3H), 7.54(m, 1H), 7.90 (d, J = 8.9 Hz, 2H). Anal. ($C_{32}H_{27}ClN_2O_4$): C, H, N.

Methyl [4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]phenyl]acetate (81). The Mitsunobu procedure used to synthesize **132** was applied to **75** and methyl (4-hydroxyphenyl)acetate to afford **81**, which was used without further purification.

[4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]phenyl]acetic Acid (82). Compound **81** was hydrolyzed according to the general procedure to afford **82** in 85% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 3.11 (t, J = 6.7 Hz, 2H), 3.45 (s, 2H), 4.07 (t, J = 6.7 Hz, 2H), 6.69 (d, J = 8.9 Hz, 1H), 6.81−6.83 (m, 3H), 6.87 (s, 1H), 7.03−7.18 (m, 7H), 7.28−7.39 (m, 6H), 7.59 (d, J = 2.0 Hz, 1H). Anal. ($C_{32}H_{28}ClNO_3$): C, H, N.

Methyl 3-[4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]phenyl]propanoate (83). The Mitsunobu procedure used to synthesize **132** was applied to **75** and methyl 3-(4-hydroxyphenyl)propanoate to afford **83**, which was used without further purification.

3-[4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]phenyl]propanoic Acid (84). Compound **83** was hydrolyzed according to the general procedure to yield **84** in 90% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.63 (t, J = 7.8 Hz, 2H), 2.89 (t, J = 7.8 Hz, 2H), 3.16 (t, J = 7.2 Hz, 2H), 4.08 (t, J = 7.2 Hz, 2H), 6.54 (d, J = 9.0 Hz, 1H), 6.76−6.84 (m, 3H), 6.87 (s, 1H), 7.07−7.10 (m, 6H), 7.31 (m, 6H), 7.50 (d, J = 2.4 Hz, 1H). Anal. ($C_{33}H_{30}ClNO_3$): C, H, N.

Methyl 4-[4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]phenyl]butanoate (85). The Mitsunobu procedure used to synthesize **132** was applied to **75** and methyl 4-(4-hydroxyphenyl)butanoate to afford **85** which was used without further purification.

4-[4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]phenyl]butanoic Acid (86). Compound **85** was hydrolyzed according to the general procedure to yield **86** in 92% yield: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (quintet, J = 5.6 Hz, 2H), 2.29 (s, 3H), 2.35 (t, J = 5.6 Hz, 2H), 2.60 (t, J = 5.6 Hz, 2H), 3.16 (t, J = 5.4 Hz, 2H), 4.08 (t, J = 5.4 Hz, 2H), 6.54 (d, J = 6.6 Hz, 1H), 6.77−6.81 (m, 3H), 6.87 (s, 1H), 7.05−7.10 (m, 6H), 7.31 (m, 6H), 7.50 (d, J = 1.5 Hz, 1H); HRMS calcd for $C_{34}H_{33}ClNO_3$ $(M + H)^+$ 538.21435, found 538.21361. Anal. ($C_{34}H_{32}ClNO_3$): C, H, N.

Methyl 2-Chloro-4-[2-[5-chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoate (87). The Mitsunobu procedure used to synthesize **132** was applied to **75** and methyl 2-chloro-4-hydroxybenzoate[111] to afford **87**, which was used without further purification.

2-Chloro-4-[2-[5-chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoic Acid (88). Compound **87** was hydrolyzed according to the general procedure to yield **88** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.19 (t, J = 5.3 Hz, 2H), 4.17 (t, J = 5.3 Hz, 2H), 6.55 (d, J = 6.7 Hz, 1H), 6.77 (dd, J = 6.6, 1.9 Hz, 1H), 6.82 (dd, J = 6.6, 1.6 Hz, 1H), 6.87 (s, 1H), 6.92 (d, J = 1.8 Hz, 1H), 7.07−7.09 (m, 4H), 7.30−7.32 (m, 6H), 7.49 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 6.6 Hz, 1H); HRMS calcd for $C_{31}H_{26}Cl_2NO_3$ $(M + H)^+$ 530.1284, found 530.1271.

Methyl 4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]-2-fluorobenzoate (89). The Mitsunobu procedure used to synthesize **132** was applied to **75** and methyl 2-fluoro-4-hydroxybenzoate[112] to afford **89**, which was used without further purification.

4-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]-2-fluorobenzoic Acid (90). Compound **89** was hydrolyzed according to the general procedure to afford **90** in 94% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.20 (t, J = 5.2 Hz, 2H), 4.17 (t, J = 5.2 Hz, 2H), 6.55 (d, J = 6.6 Hz, 1H), 6.60 (dd, J = 9.6, 3.0 Hz, 1H), 6.67 (dd, J = 6.6, 1.7 Hz, 1H), 6.82 (dd, J = 6.6, 1.5 Hz, 1H), 6.87 (s, 1H), 7.07−7.09 (m, 4H), 7.30−7.32 (m, 6H), 7.49 (d, J = 1.5 Hz, 1H), 7.93 (t, J = 6.5 Hz, 1H). HRMS calcd for $C_{33}H_{30}ClFNO_3$ $(M + H)^+$ 514.15798, found 514.15796.

3-(2-Bromoethyl)-5-chloro-1-(diphenylmethyl)-2-methyl-1*H*-indole (91). To **75** (1.0 equiv) and 1,3-bis(diphenylphosphino)-propane (0.8 equiv) in CH_2Cl_2 (0.15 M) at 0 °C was added carbon tetrabromide (1.3 equiv). The reaction was warmed to room temperature, stirred for 1 h, poured into ethyl ether, and filtered. The filtrate was evaporated and the residue diluted with ethyl ether, filtered, concentrated, and purified by flash chromatography to afford **91** in 76% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.13 (t, J = 7.8 Hz, 2H), 3.41 (t, J = 7.9 Hz, 2H), 6.42 (d, J = 8.8 Hz, 1H), 6.69 (dd, J = 8.8, 2.1 Hz, 1H), 6.69 (s, 1H), 6.75 (s, 1H), 6.97 (m, 4H), 7.17 (m, 5H), 7.33 (d, J = 1.8 Hz, 1H).

Methyl 3-[4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]thio]phenyl]propanoate (92). Compound **91** was mixed with methyl 3-(4-mercaptophenyl)propanoate (1.5 equiv) and K_2CO_3 (1.5 equiv) in DMF (0.6 M). The resulting mixture was stirred at room temperature for 2 h and then H_2O was added, followed by EtOAc extraction and flash chromatography to afford **92** in 82% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.62 (t, J = 7.9 Hz, 2H), 2.95 (m, 4H), 3.11 (m, 2H), 3.66 (s, 3H), 6.52 (d, J = 9.1 Hz, 1H), 6.79 (dd, J = 8.7, 2.3 Hz, 1H), 6.84 (s, 1H), 7.08 (m, 4H), 7.13 (d, J = 8.3 Hz, 2H), 7.30 (m, 8H), 7.34 (d, J = 2.3 Hz, 2H).

Methyl 3-[4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]phenyl]propanoate (93). Compound **92** (1.0 equiv) was dissolved in CH_3CN (0.01 M), and then molecular sieves (powder, 4 Å) and NMO (3.0 equiv) were added under N_2, followed by TPAP (0.05 equiv). The resulting mixture was heated to 40 °C for 3 h, concentrated, and purified to yield 25% of **93**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (m, 3H), 2.68 (m, 2H), 3.09 (m, 4H), 3.28 (m, 2H), 3.67 (m, 3H), 6.50 (d, J = 9.1 Hz, 1H), 6.77 (dd, J = 8.7, 1.9 Hz, 1H), 6.81 (s, 1H), 7.05 (m, J = 5.7 Hz, 4H), 7.10 (d, J = 1.9 Hz, 1H), 7.30 (m, 6H), 7.42 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H).

3-[4-[[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]phenyl]propanoic Acid (94). Compound **93** was hydrolyzed according to the general procedure to afford **94** in 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.72 (t, J = 7.0 Hz, 2H), 3.05 (t, J = 7.0 Hz, 2H), 3.08−3.15 (m, 2 H), 3.24−3.31 (m, 2H), 6.50 (d, J = 9.0 Hz, 1H), 6.77 (dd, J = 9.0, 3.0 Hz, 1H), 6.82 (s, 1H), 7.04 (m, 4H), 7.11 (d, J = 3.0 Hz, 1H), 7.31 (m, 6H), 7.43 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H); HRMS calcd for $C_{33}H_{31}ClNO_4S$ $(M + H)^+$ 572.1657, found 572.1642. Anal. ($C_{33}H_{30}ClNO_4S$): C, H, N.

Methyl 4-[(2-Bromoethyl)sulfonyl]benzoate (95). To a solution of methyl 4-mercaptobenzoate (2 g, 11.9 mmol) in DMF (40 mL) were added 1,2-dibromoethane (7 mL, 82 mmol) and K_2CO_3 (1.6 g, 11.9 mmol). The reaction was stirred for 2 h at room temperature, diluted with EtOAc, washed with brine, dried, filtered, and concentrated to afford the crude sulfide which was used without purification. 4-(2-Bromoethylsulfanyl)benzoic acid methyl ester (1 equiv) was dissolved in MeOH:acetone:H_2O (8:8:5) and then treated with Oxone (3 equiv). After 90 min the reaction mixture was diluted with $CHCl_3$, washed with H_2O and brine, and dried over Na_2SO_4, and concentrated to yield **95** of purity sufficient to carry on to the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (t, J = 7.7 Hz, 2H), 3.50 (t, J = 7.1 Hz, 2H), 3.86 (s, 3H), 7.88 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H).

Methyl 4-(Vinylsulfonyl)benzoate (96). Compound **95** (1 equiv) was dissolved in CH_2Cl_2 (0.5 M) and then treated with NEt_3 (1.5 equiv). After 30 min of stirring, the reaction was diluted with EtOAc and brine, the layers were separated, and the organic layer was dried over Na_2SO_4 and concentrated to afford **96** in quantitative crude yield that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.00 (d, J = 9.5 Hz, 1H), 6.40

(d, J = 16.5 Hz, 1H), 6.54 (dd, J = 16.5, 9.5 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H).

6-Chloro-2-methyl-1*H*-indole (97) and 4-Chloro-2-methyl-1*H*-indole (98). 3-Chlorophenylhydrazine hydrochloride and acetone were treated as in the general Fischer indole procedure to afford 6-chloro-2-methyl-1*H*-indole (**97**) in 20% yield and 4-chloro-2-methyl-1*H*-indole (**98**) in 7% yield. For **98**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.22 (s, 1H), 6.93 (m, 2H), 7.04 (m, 1H) 7.80 (br s, 1H).

Methyl4-[[2-(6-Chloro-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]-benzoate (105). Compounds **97** and **96** were treated under the general Zn salt alkylation conditions to afford **105** in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.01 (dd, J = 8.2, 5.2 Hz, 2H), 3.27 (dd, J = 8.1, 5.3 Hz, 2H), 3.85 (s, 3H), 6.85 dd, J = 8.4, 2.0 Hz, 1H), 7.00 (m, 2H), 7.63 (br s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H).

Methyl 4-[[2-[6-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (113). Compound **105** was N-alkylated as described in the general procedure to give **113** in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.03 (m, 2H), 3.21 (m, 2H), 3.85 (s, 3H), 6.49 (d, J = 1.6 Hz, 1H), 6.69 (s, 1H), 6.82 (dd, J = 1.8, 8.4 Hz, 1H), 6.92 (m, 4H), 7.06 (dd, J = 1.8, 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.19 (m, 6H), 7.89 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.7 Hz, 2H).

4-[[2-[6-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]sulfonyl]benzoic Acid (114). Compound **113** was hydrolyzed according to the general procedure in 95% yield: ^{1}H NMR (DMSO-d_6) δ 1.93 (s, 3H), 2.81 (m, 2H), 3.37 (m, 2H), 6.53 (d, J = 1.5, 1H), 6.76 (dd, J = 8.4, 1.8, 1H), 6.88 (m, 4H), 7.01 (s, 1H), 7.12 (d, J = 8.4, 1H), 7.21 (m, 2H), 7.78 (d, J = 8.2, 2H), 7.99 (d, J = 8.0, 2H).

Methyl4-[[2-(4-Chloro-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]-benzoate (106). Compounds **98** and **96** were treated under the general Zn salt alkylation conditions to afford **106** in 24% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.14 (m, 2H), 3.39 (m, 2H), 3.84 (s, 3H), 6.79 (m, 2H), 6.94 (m, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.88 (br s, 1H), 8.01 (d, J = 8.4 Hz, 2H).

Methyl 4-[[2-[4-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (115). Compound **106** was N-alkylated as described in the general procedure to afford **115** in 25% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.23 (m, 2H), 3.33 (m, 2H), 3.86 (s, 3H), 6.49 (d, J = 8.4 Hz, 1H), 6.60 (t, J = 8.3 Hz, 1H), 6.76 (m, 2H), 6.94 (m, 4H), 7.18 (m, 6H), 7.93 (d, J = 8.3 Hz, 2H), 8.10 (d, J = 8.3 Hz, 2H).

4-[[2-[4-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]sulfonyl]benzoic Acid (116). Compound **115** was hydrolyzed according to the general procedure to afford **116** in 96% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.99 (s, 3H), 3.04 (m, 2H), 3.88 (m, 2H), 6.61 (m, 2H), 6.73 (dd, J = 6.0, 4.0 Hz, 1H), 6.91 (d, J = 6.2 Hz, 2H), 7.07 (s, 1H), 7.20 (m, 6H), 7.80 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H).

Methyl 4-[[2-(2-Methyl-1*H*-indol-3-yl)ethyl]sulfonyl]benzoate (107). 2-Methylindole and **96** were treated under the general Zn salt alkylation conditions to afford **107** in 73% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.16 (m, 2H), 3.40 (m, 2H), 3.97 (s, 3H), 7.05 (m, 2H), 7.20 (m, 2H), 7.73 (s, 1H), 7.93 (d, J = 8.7 Hz, 2H), 8.13 (d, J = 8.7 Hz, 2H).

Methyl 4-[[2-[1-(Diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (117). Compound **107** was N-alkylated as described in the general procedure to afford **117** in 25% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.19 (m, 2H), 3.35 (m, 2H), 3.98 (s, 3H), 6.67 (d, J = 8.2 Hz, 1H), 6.86 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 7.08 (m, 4H), 7.29 (m, 6H), 8.04 (d, J = 8.1 Hz, 2H), 8.22 (d, J = 8.5 Hz, 2H).

4-[[2-[1-(Diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoic Acid (118). Compound **117** was hydrolyzed according to the general procedure to afford **118** in 30% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.21 (m, 2H), 3.37 (m, 2H), 6.55 (d, J = 8.4 Hz, 1H), 6.86 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 7.08 (m, 4H), 7.29 (m, 6H), 8.07 (d, J = 8.5 Hz, 2H), 8.28 (d, J = 8.4 Hz, 2H).

7-Chloro-2-methyl-1*H*-indole (100). 2-Chlorophenylhydrazine hydrochloride and acetone were treated as in the general Fischer indole procedure to afford **100** in 20% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.15 (s, 1H), 6.89 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.3 (d, J = 7.6 Hz, 1H), 7.95 (br s, 1H).

Methyl4-[[2-(7-Chloro-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]-benzoate (108). Compounds **100** and **96** were treated under the general Zn salt alkylation conditions to afford **108** in 11% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.02 (m, 2H), 3.30 (m, 2H), 3.85 (s, 3H), 6.82 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.80 (s, 1H), 7.95 (d, J = 8.6 Hz, 2H).

Methyl 4-[[2-[7-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (119). Compound **108** was N-alkylated as described in the general procedure to afford **119** in 15% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H), 2.99 (m, 2H), 3.16 (m, 2H), 3.85 (s, 3H), 6.86 (t, J = 7.7 Hz, 1H), 6.96 (m, 4H), 7.08 (m, 4H), 7.15 (m, 6H), 7.87 (d, J = 8.6 Hz, 2H), 8.09 (d, J = 8.6 Hz, 2H), 8.37 (s, 1H).

4-[[2-[7-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethyl]sulfonyl]benzoic Acid (120). Compound **119** was hydrolyzed according to the general procedure to afford **120** in 95% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (s, 3H), 2.84 (t, J = 8.0 Hz, 2H), 3.46 (t, J = 8.0 Hz, 2H), 6.89 (m, 5H), 7.21 (m, 7H), 7.89 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.70 (br s, 1H).

5,6-Dichloro-2-methyl-1*H*-indole (101) and 4,5-Dichloro-2-methyl-1*H*-indole (102). 3,4-Dichlorophenylhydrazine hydrochloride and acetone were treated as in the general Fischer indole procedure to yield two products after isolation; **101** was the major product in 35% yield and the minor product **102** was isolated in 25% yield. For **101**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.02 (s, 1H), 7.22 (s, 1H), 7.44 (s, 1H), 7.71 (br s, 1H). For **102**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 6.19 (s, 1H), 6.98 (m, 2H), 7.88 (br s, 1H).

Methyl 4-[[2-(5,6-Dichloro-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]benzoate (109). Compound **101** and **96** were treated under the general Zn salt alkylation conditions to afford **109** in 46% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.99 (m, 2H), 3.26 (m, 2H), 3.86 (s, 3H), 7.11 (s, 1H), 7.14 (s, 1H), 7.64 (br s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.99 (d, J = 8.2 Hz, 2H).

Methyl 4-[[2-[5,6-Dichloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (121). Compound **109** was N-alkylated as described in the general procedure to afford **121** in 51% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.02 (m, 2H), 3.20 (m, 2H), 3.85 (s, 3H), 6.52 (s, 1H), 6.66 (s, 1H), 6.91 (m, 4H), 7.21 (m, 7H), 7.89 (d, J = 8.6 Hz, 2H), 8.09 (d, J = 8.6 Hz, 2H).

4-[[2-[5,6-Dichloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoic Acid (122). Compound **121** was hydrolyzed according to the general procedure to afford **122** in 96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.02 (m, 2H), 3.22 (m, 2H), 6.52 (s, 1H), 6.66 (s, 1H), 6.91 (m, 4H), 7.20 (m, 7H), 7.94 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H).

Methyl 4-[[2-(4,5-Dichloro-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]benzoate (110). Compound **102** and **96** were treated under the general Zn salt alkylation conditions to afford **110** in 34% yield.

Methyl 4-[[2-[4,5-Dichloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (123). Compound **110** was N-alkylated as described in the general procedure to afford **123** in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 3.27 (m, 4H), 3.86 (s, 3H), 6.37 (d, J = 8.8 Hz, 1H), 6.73 (m, 4H), 6.92 (m, 4H), 7.19 (m, 6H), 7.92 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 8.6 Hz, 2H).

4-[[2-[4,5-Dichloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoic Acid (124). Compound **123** was hydrolyzed according to the general procedure to afford **124** in 92% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03 (s, 3H), 3.05 (m, 2H), 3.40 (m, 2H), 6.58 (d, J = 8.8, 1H), 6.88 (m, 5H), 7.10 (s, 1H), 7.22 (m, 6H), 7.91 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H).

5-Fluoro-2-methyl-1*H*-indole (103). 4-Fluorophenylhydrazine hydrochloride and acetone were treated as in the general Fischer indole procedure to yield 40% of **103** after column chromatography: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 6.06 (s, 1H), 6.72 (dt, J = 2.7, 9.0 Hz, 1H), 7.04 (m, 2H), 7.72 (br s, 1H).

Methyl 4-[[2-(5-Fluoro-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]-benzoate (111). Compounds **103** and **96** were treated under the general Zn salt alkylation conditions to afford **111** in 45% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.99 (m, 2H), 3.25 (m, 2H), 3.85 (s, 3H), 6.70 (m, 2H), 6.95 (dd, J = 4.0, 9.0 Hz, 1H), 7.62 (br s, 1H), 7.80 (d, J = 9.0 Hz, 2H), 8.00 (d, J = 9.0 Hz, 2H).

Methyl 4-[[2-[1-(Diphenylmethyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (125). Compound **111** was N-alkylated as described in the general procedure to afford **125** in 25% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.03 (m, 2H), 3.22 (m, 2H), 3.86 (s, 3H), 6.42 (m, 2H), 6.71 (s, 1H), 6.78 (dd, J = 2.0, 9.0 Hz, 1H), 6.93 (m, 4H), 7.17 (m, 7H), 7.91 (d, J = 9.0 Hz, 2H), 8.11 (d, J = 9.0 Hz, 2H).

4-[[2-[1-(Diphenylmethyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]-ethyl]sulfonyl]benzoic Acid (126). Compound **125** was hydrolyzed according to the general procedure to afford **126** in 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.05 (m, 2H), 3.22 (m, 2H), 6.46 (m, 2H), 6.70 (s, 1H), 6.78 (d, J = 9.2 Hz, 1H), 6.94 (m, 4H), 7.16 (m, 6H) 7.94 (d, J = 8.4 Hz, 2H), 8.17 (d, J = 8.0 Hz, 2H).

Methyl 4-[[2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)ethyl]sulfonyl]benzoate (112). Compounds **104** and **96** were treated under the general Zn salt alkylation conditions to afford **112** in 62% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.11 (m, 2H), 3.37 (m, 2H), 3.80 (s, 3H), 3.97 (s, 3H), 6.67 (s, 1H), 6.67 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 7.63 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 8.14 (d, J = 8.0 Hz, 2H).

Methyl 4-[[2-[1-(Diphenylmethyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]ethyl]sulfonyl]benzoate (127). Compound **112** was N-alkylated as described in the general procedure to afford **127** in 23% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.17 (m, 2H), 3.33 (m, 2H), 3.75 (s, 3H), 3.97 (s, 3H), 6.37 (s, 2H), 6.57 (s, 1H), 6.63 (s, 1H), 6.93 (m, 4H), 7.32 (m, 6H), 8.04 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 8.7 Hz, 2H).

4-[[2-[1-(Diphenylmethyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-ethyl]sulfonyl]benzoic Acid (128). Compound **127** was hydrolyzed according to the general procedure to afford **128** in 56% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.17 (m, 2H), 3.36 (m, 2H), 3.77 (s, 3H), 6.50 (s, 2H), 6.71 (s, 1H), 6.79 (s, 1H), 7.07 (m, 4H), 7.29 (m, 6H), 8.08 (d, J = 8.1 Hz, 2H), 8.29 (d, J = 8.5 Hz, 2H).

Methyl (6-Chloro-2-methyl-1*H*-indol-3-yl)oxoacetate (129). 6-Chloro-1*H*-indole was treated as in the general oxoacetate procedure to generate **129** in 89% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.86 (s, 3H), 7.11 (dd, J = 8.6, 1.9 Hz, 1H), 7.21 (d, J = 1.9 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 8.5 (br s, 1H).

2-(6-Chloro-2-methyl-1*H*-indol-3-yl)ethanol (130). Compound **129** (1.0 equiv) was dissolved in 10 mL of anhydrous THF and cooled in an ice bath. $LiAlH_4$ (4 equiv of a 1.0 M solution in THF) was added dropwise, the reaction temperature being kept below 10 °C. The reaction was stirred for 30 min, at which point a standard basic workup was performed and the filtrate evaporated to result in isolation of **130** as a clear oil in 99% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.81 (t, J = 6.4 Hz, 1H), 3.69 (q, J = 6.4 Hz, 1H), 6.92 (dd, J = 8.4 Hz, 1.9, 1H), 7.11 (d, J = 1.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.78 (br s, 1H).

2-[6-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethanol (131). Compound **130** was N-alkylated as described in the general procedure to generate **131** in 17% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.85 (t, J = 6.6 Hz, 2H), 3.69 (t, J = 6.6 Hz, 2H), 6.53 (d, J = 1.8 Hz, 1H), 6.76 (s, 1H), 6.87 (dd, J = 8.4,1.8 Hz, 1H), 6.98 (m, 4H), 7.21 (m, 6H), 7.31 (d, J = 8.5 Hz, 1H).

Methyl 4-[2-[6-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoate (132). Compound **131** (1.0 equiv) and PPh_3 (1.2 equiv) were dissolved in 2 mL of CH_2Cl_2. To this solution were added methyl 4-hydroxybenzoate (1.0 equiv) and diisopropyl azodicarboxylate (1.1 equiv), and the reaction was stirred for 16 h. The reaction was diluted with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **132** in 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.09 (t, J = 7.1, 2H), 3.78 (s, 3H), 4.04 (t, J = 7.1 Hz, 2H), 6.55 (d, J = 1.7 Hz, 1H), 6.72 (m, 3H), 6.89 (dd, J = 8.4, 1.5 Hz, 1H), 6.97 (m, 5H), 7.20 (m, 6H), 7.33 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.6 Hz, 2H).

4-[2-[6-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (133). Compound **132** was hydrolyzed according to the general procedure to afford **133** in 97% yield: ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 2.99 (t, J = 6.9, 2H), 4.00 (t, J = 6.9, 2H), 6.70 (d, J = 1.8, 1H), 6.70 (d, J = 8.5, 2H), 6.82 (dd, J = 8.2, 1.7, 1H), 6.92 (m, 4H), 7.07 (s, 1H), 7.22 (s, 6H), 7.43 (d, J = 8.4, 1H), 7.68 (d, J = 8.0, 2H).

Ethyl (5-Bromo-2-methyl-1*H*-indol-3-yl)acetate (134). 4-Bromophenylhydrazine hydrochloride and ethyl levulinate were treated as in the general Fischer indole procedure to afford **134** in 60% yield after flash chromatography: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 3.62 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.11 (d, J = 8.5 Hz, 1H), 7.19 (m, 1H), 7.65 (s, 1H), 7.93 (s, 1H).

Ethyl [5-Bromo-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-acetate (135). Compound **134** was N-alkylated as described in the general procedure to generate **135** in 72% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 3.66 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 6.49 (d, J = 9.1 Hz, 1H), 6.87 (s, 1H), 6.93 (dd, J = 8.8, 1.9 Hz, 1H), 7.10 (m, 4 H), 7.33 (m, 6H), 7.68 (d, J = 1.9 Hz, 1 H).

2-[5-Bromo-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethanol (136). To **135** (1.0 equiv) in THF (0.04 M) at 0 °C was added a 1.0 M solution of $LiAlH_4$ (2.0 equiv). A standard basic workup was performed when TLC analysis indicated consumption of the starting material. The mixture was dried and concentrated to give **136** in 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.97 (t, J = 6.5 Hz, 2H), 3.82 (t, J = 6.6 Hz, 2H), 6.49 (d, J = 8.8 Hz, 1H), 6.87 (s, 1H), 6.93 (dd, J = 8.8, 1.92 Hz, 1H), 7.09 (m, 4H), 7.34 (m, 6H), 7.65 (d, J = 1.9 Hz, 1H).

Methyl 4-[2-[5-Bromo-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoate (137). A solution of **136** (1.0 equiv), methyl 4-hydroxybenzoate (1.0 equiv), and polystyrene-bound PPh_3 (1.5 equiv) in CH_2Cl_2 (0.03 M) was stirred for 1 h and then diisopropyl azodicarboxylate (1.1 equiv) was added. The mixture was filtered when TLC analysis indicated the consumption of the starting material. The filtrate was washed with H_2O and brine, dried, concentrated, and purified by column chromatography to give **137** in 74% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.19 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 4.16 (t, J = 7.1 Hz, 2H), 6.50 (d, J = 8.8 Hz, 1H), 6.85 (m, J = 8.8 Hz, 3H), 6.94 (dd, J = 8.8, 1.9 Hz, 1H), 7.09 (m, 4H), 7.31 (m, 6H), 7.67 (d, J = 1.9 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H).

4-[2-[5-Bromo-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (138). Compound **137** was hydrolyzed in 93% yield according to the general procedure: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.19 (t, J = 7.0 Hz, 2H), 4.19 (t, J = 6.9 Hz, 2H), 6.50 (d, J = 8.7 Hz, 1H), 6.87 (m, 3H), 7.01 (d, J = 9.0 Hz, 1H), 7.09 (m, 4H), 7.30 (m, 6H), 7.67 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 8.9 Hz, 2H); HRMS calcd for $C_{31}H_{26}BrNO_3$ + H 540.11689, found 540.11667.

Methyl 4-[2-[1-(Diphenylmethyl)-2-methyl-5-phenyl-1*H*-indol-3-yl]ethoxy]benzoate[99] (139). Compound **137** (1.0 equiv), phenylboronic acid (1.5 equiv), KF (3 equiv), palladium acetate (0.01 equiv), and biphenyl-3-yldi-*tert*-butylphosphane (0.02 equiv) were diluted with THF and stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl ether, washed with 1 N NaOH, dried over Na_2SO_4, and concentrated to give a brown oil. Purification using flash chromatography gave **139** in 65%

yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.29 (t, J = 7.2 Hz, 2H), 3.88 (s, 3H), 4.21 (t, J = 7.3 Hz, 2H), 6.74 (d, J = 8.5 Hz, 1H), (6.86 (d, J = 8.8 Hz, 2H), 6.94 (s, 1H), 7.15 (m, 4H), 7.32 (m, 7H), 7.40 (t, J = 7.7 Hz, 3H), 7.60 (d, J = 7.4 Hz, 2H), 7.74 (d, J = 1.1 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H).

4-[2-[1-(Diphenylmethyl)-2-methyl-5-phenyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (140). Compound **139** was hydrolyzed according to the general procedure to afford **140** in 80% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.30 (t, J = 7.1 Hz, 2H), 4.23 (t, J = 7.4 Hz, 2H), 6.74 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.94 (s, 1H), 7.16 (m, 4H), 7.32 (m, 7H), 7.40 (t, J = 7.7 Hz, 3H), 7.61 (d, J = 7.4 Hz, 2H), 7.75 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H).

Methyl 4-[2-[1-(Diphenylmethyl)-2-methyl-5-morpholin-4-yl-1*H*-indol-3-yl]ethoxy]benzoate (141).[100] Compound **137** (1.0 equiv), tris(dibenzylideneacetone)dipalladium(0) (0.0025 equiv), biphenyl-3-yldi-*tert*-butylphosphine (0.01 equiv), and NaO-*t*Bu (1.4 equiv) were diluted with toluene (0.27 M). Morpholine (1.2 equiv) was added and the reaction was heated at 80 °C for 1 d. The reaction was cooled, diluted with ethyl ether, and filtered through Celite and concentrated. Purification using flash chromatography gave **141** in 27% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.10 (m, 4H), 3.21 (t, J = 7.6 Hz, 2H), 3.85 (m, J = 4.1 Hz, 4H), 3.88 (s, 3H), 4.16 (t, J = 8.1 Hz, 2H), 6.59 (m, 2H), 6.87 (m, 3H), 7.03 (s, 1H), 7.11 (m, 4H), 7.31 (m, 6H), 7.96 (d, J = 8.8 Hz, 2 H).

4-[2-[1-(Diphenylmethyl)-2-methyl-5-morpholin-4-yl-1*H*-indol-3-yl]ethoxy]benzoic Acid (142). Compound **141** was hydrolyzed according to the general procedure to afford **142** in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.13 (s, 4H), 3.22 (t, J = 7.1 Hz, 2H), 3.88 (s, 4H), 4.18 (t, J = 7.0 Hz, 2H), 6.60 (m, 2H); HRMS calcd for $C_{35}H_{34}N_2O_4$ 546.25186, found (ESI+) 547.25914.

1-(Diphenylmethyl)-2-methyl-5-nitro-1*H*-indole (144). 2-Methyl-5-nitroindole was N-alkylated as described in the general procedure to generate **144** in 23% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 5.79 (s, 1H), 7.25 (m, 10H), 7.93 (s, 1H), 7.99 (dd, J = 8.8, 1.9 Hz, 1H), 8.18 (s, 1H).

Ethyl [1-(Diphenylmethyl)-2-methyl-5-nitro-1*H*-indol-3-yl]-oxoacetate (145). Following the procedure to form indole oxoacetates, **144** was treated with chlorooxoacetic acid ethyl ester, which generated **145** in 32% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, J = 7.2 Hz, 3H), 2.71 (s, 3H), 4.53 (q, J = 7.1 Hz, 2H), 6.80 (d, J = 9.5 Hz, 1H), 7.05 (s, 1H), 7.11 (m, 4H), 7.39 (m, 6H), 7.87 (dd, J = 10.5, 2.34 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H).

2-[1-(Diphenylmethyl)-2-methyl-5-nitro-1*H*-indol-3-yl]ethanol (146). Compound **145** (1.0 equiv) was diluted with THF, and a 2.0 M solution of borane−methyl sulfide complex in THF (1.5 equiv) was added dropwise. The reaction was heated at reflux for 20 h. It was quenched with 1 N NaOH and then partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated to give a yellow solid. Purification using flash chromoatography gave **146** in 50% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.05 (t, J = 6.9 Hz, 2H), 3.87 (t, J = 6.2 Hz, 2H), 6.62 (d, J = 9.1 Hz, 1H), 6.92 (s, 1H), 7.10 (m, 4H), 7.34 (m, 6H), 7.76 (dd, J = 9.2, 2.2 Hz, 1H), 8.48 (d, J = 1.2 Hz, 1H).

Methyl 4-[2-[1-(Diphenylmethyl)-2-methyl-5-nitro-1*H*-indol-3-yl]ethoxy]benzoate (147). Using the Mitsunobu procedure for the synthesis of **132**, **146** and methyl 4-hydroxybenzoate gave **147** in 63% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.27 (t, J = 6.7 Hz, 2H), 3.88 (s, 3H), 4.22 (t, J = 6.5 Hz, 2H), 6.63 (d, J = 9.1 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 6.92 (s, 1H), 7.08 (m, 4H), 7.34 (m, 6H), 7.77 (dd, J = 9.1, 2.3 Hz, 1H), 7.95 (d, J = 8.9 Hz, 2H), 8.56 (d, J = 2.3 Hz, 1H).

4-[2-[1-(Diphenylmethyl)-2-methyl-5-nitro-1*H*-indol-3-yl]ethoxy]-benzoic Acid (148). Compound **147** was hydrolyzed according to the general procedure to afford **148** in 44% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.28 (t, J = 6.5 Hz, 2 H), 4.24 (t, J = 6.6 Hz, 2 H), 6.63 (d, J = 9.1 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.93 (s, 1 H), 7.08 (m, 4 H), 7.34 (m, 6 H), 7.78 (dd, J = 9.2, 2.1 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 2 H), 8.57 (d, J = 1.9 Hz, 1 H); HRMS calcd for $C_{31}H_{26}N_2O_5$ 506.18417, found (ESI+) 507.19102.

Methyl 4-[2-[5-Amino-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoate (149). Compound **147** was reduced using catalytic palladium on carbon (10% weight) and H_2 (1 atm), which after filtration and purification gave **149** in 48% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.99 (t, J = 7.4 Hz, 2H), 3.70 (s, 3H), 3.97 (t, J = 7.4 Hz, 2H), 6.20 (dd, J = 8.5, 2.2 Hz, 1H), 6.30 (m, 1H), 6.68 (m, 3H), 6.72 (d, J = 1.9 Hz, 1H), 6.94 (m, 4H), 7.12 (m, 6H), 7.78 (d, J = 8.8 Hz, 2 H).

4-[2-[5-Amino-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (150). Compound **149** was hydrolyzed according to the general procedure to afford **150** in 74% yield: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.48 (s, 3H), 3.36 (t, J = 7.0 Hz, 2H), 4.40 (t, J = 6.8 Hz, 2H), 6.38 (dd, J = 8.7, 1.8 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 7.11 (d, J = 9.1 Hz, 2H), 7.24 (s, 1H), 7.32 (m, 4H), 7.50 (m, 6H), 8.09 (d, J = 8.8 Hz, 2H); HRMS calcd for $C_{31}H_{28}N_2O_3$ 476.20999, found (ESI+) 477.21683.

General Procedure for Treatment of 91 with Phenols: **Methyl 3-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]-benzoate (151).** A solution of methyl 3-hydroxybenzoate (1.2 equiv) in DMSO (0.5 M) was added to NaH (60% oil dispersion of sodium hydride, 1.4 equiv) in DMSO (1 M). The reaction mixture was stirred for 15 min and then **91** (1 equiv) in DMSO (1 M) was added. The reaction was then heated at 80 °C for 18 h. The mixture was poured into EtOAc, washed with H_2O and brine, concentrated, and purified to give **151** in 23% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.07 (t, J = 7.2 2H), 3.77 (s, 3H), 4.04 (t, J = 7.1 Hz, 2H), 6.43 (d, J = 8.8 Hz, 1H), 6.69 (dd, J = 8.8, 2.2 Hz, 1H), 6.75 (s, 1H), 6.95 (m, 5H), 7.19 (m, 5H), 7.39 (m, 2H), 7.49 (d, J = 7.5 Hz, 1H).

3-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]benzoic Acid (152). Compound **151** was hydrolyzed according to the general procedure to afford **152** in 98% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.27 (s, 3H), 3.14 (t, J = 6.4 Hz, 2H), 4.17 (t, J = 6.4 Hz, 2H), 6.69 (s, 1H), 6.71 (s, 1H), 6.81−6.84 (m, 2H), 7.08 (d, J = 7.3 Hz, 1H), 7.12 (dd, J = 8.2, 2.6 Hz, 2H), 7.18 (s, 1H), 7.28−7.39 (m, 7H), 7.50 (d, J = 8.0 Hz, 2H), 7.62 (s, 1H).

Methyl 3-Chloro-4-[2-[5-chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoate (153). Following the general procedure used for the synthesis of **151**, methyl 3-chloro-4-hydroxybenzoate was treated with **91** to yield **153** in 28% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.14 (t, J = 6.5 Hz, 2H), 3.76 (s, 3H), 4.14 (t, J = 6.5 Hz, 2H), 6.45 (d, J = 8.9 Hz, 1H), 6.72 (m, 3H), 6.98 (m, 5H), 7.19 (m, 5H), 7.41 (d, J = 1.8 Hz, 1H), 7.74 (dd, J = 8.7, 2.1 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H).

3-Chloro-4-[2-[5-chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]benzoic Acid (154). Compound **153** was hydrolyzed according to the general procedure to afford **154** in 94% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.27 (s, 3H), 3.19 (t, J = 6.1 Hz, 2H), 4.31 (t, J = 6.1 Hz, 2H), 6.70 (s, 1H), 6.72 (s, 1H), 6.81−6.84 (m, 1H), 7.06−7.10 (m, J = 6.7 Hz, 2H), 7.17−7.20 (m, 1H), 7.30−7.38 (m, 7H), 7.66−7.67 (m, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.86−7.87 (m, 1H).

6-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]nicotinic Acid (155). Following the general procedure used for **151**, except with 2.5 equiv of sodium hydride, **91** and 6-hydroxynicotinic acid gave **155** in 5% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.23 (s, 3H), 3.08 (t, J = 6.7 Hz, 2H), 4.36 (t, J = 6.7 Hz, 2H), 6.31 (d, J = 9.8 Hz, 1H), 6.68 (d, J = 9.2 Hz, 1H), 6.82 (dd, 1H), 7.03−7.07 (m, J = 6.1 Hz, 2H), 7.16 (s, 1H), 7.31−7.37 (m, 8H), 7.60 (d, J = 2.44 Hz, 1H), 7.68 (dd, J = 9.8, 2.4 Hz, 1H), 7.96 (s, 1H).

Methyl 3-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]ethoxy]isoxazole-5-carboxylate (156). Following the general procedure used for **151**, methyl 3-hydroxyisoxazole-5-carboxylate was treated with **91** to give **156** in 19% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.07 (t, J = 7.3, 2H), 3.82 (s, 3H), 4.30 (t,

J = 7.3 Hz, 2H), 6.40 (m, 2H), 6.68 (dd, J = 8.9, 2.1 Hz, 1H), 6.74 (s, 1H), 6.97 (m, 4H), 7.19 (m, 6H) 7.38 (d, J = 1.9 Hz, 1H).

3-[2-[5-Chloro-1-(diphenylmethyl)-2-methyl-1*H*-indol-3-yl]-ethoxy]isoxazole-5-carboxylic Acid (157). Compound **156** was hydrolyzed according to the general procedure to afford **157** in 94% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.25 (s, 3H), 3.16 (t, J = 7.0 Hz, 2H), 4.37 (t, J = 6.7 Hz, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.80−6.84 (m, 1H), 7.07 (m, 3H), 7.16 (s, 1H), 7.28−7.38 (m, 7H), 7.60 (m, 1H).

GLU Micelle Assay. The assay was carried in a 96-well format using a fluorescent plate reader with a 355-nM excitation filter and a 460-nM emission filter (Lab Systems Fluoroscan II, Helsinki, Finland). The assay buffer contained 940 μM Triton X-100, 50 mM Hepes (pH 7.4), 0.3 mM EDTA, 1 mM $CaCl_2$, and 300 mM KCl. DTPC (1,2-*O*-tetradecyl-*sn*-glycero-3-phosphocholine, Avanti) at a final concentration of 120 μM was added the day of the experiment and GLU (7-hydroxycoumarinyl-γ-linolenate or 2-oxo-2*H*-chromen-6-yl (6*Z*,9*Z*,12*Z*)-octadeca-6,9,12-trienoate, Biomol Research Lab, Inc.) at a final concentration of 90 μM was added immediately prior to each assay.

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

$$\text{percent inhibition} = [1 - (\text{slope with inhibitor} - \text{slope negative control})/(\text{slope positive control} - \text{slope negative control})] \times 100$$

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

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

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

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

Pharmacokinetics and Oral Bioavailability in Rats. Plasma concentrations of test compounds in rat plasma were measured by LC−MS/MS. The quantitation was determined from standard curves that were prepared and analyzed on each day of sample analysis. The extraction is carried out by protein precipitation using acetonitrile:serum 2:1.

Acknowledgment. We thank Jinglun Wu for help with the whole blood assay, Ravindra Kumar for MC-9 data, Katherine Lee for a critical review of the manuscript, Mike Shanler and Xin Xu for providing pharmacokinetic analysis, Walter Massefski, Ning Pan, and Nelson Huang for their analytical expertise, and Glen Larsen for insightful discussions.

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

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JM0507882