Reactions of Functionalized Sulfonamides: Application to Lowering the Lipophilicity of Cytosolic Phospholipase $A_2\alpha$ Inhibitors[||]

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The $cPLA_2\alpha$ inhibitors we reported earlier were potent in both isolated enzyme and rat whole blood assays but have high $plogD_{7.4}$. To address these issues, reactions of electrophilic sulfonamides **9**−**12** were employed to incorporate various heterocyclic or heteroatom-based reagents into $cPLA_2\alpha$ inhibitors. For example, reactions of **9** with sulfur nucleophiles such as thiophenol allowed rapid assembly of thioether analogues that were converted into the corresponding sulfoxides to afford less lipophilic derivatives. Reactions of **10** and **11** with various nitrogen nucleophiles, including aromatic heterocycles and aliphatic amines, provided an efficient way to introduce polarity into $cPLA_2\alpha$ inhibitors. Finally, we report the first application of (2-formylphenyl)methanesulfonyl chloride, **13**. Reductive amination of 2-formylphenylmethane sulfonamides allowed the introduction of various nitrogen nucleophiles. Several inhibitors obtained herein have $plogD_{7.4}$ values 3−4 units lower than previously synthesized compounds and yet maintain in vitro potency.

Introduction

Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$,[a] group IVA phospholipase) is the only phospholipase with specificity for *sn-2* arachidonyl containing membrane phospholipids.[1] Its enzymatic action generates arachidonic acid (AA) and a lysophospholipid, both of which are precursors to proinflammatory molecules including prostaglandins (PGs), leukotrienes (LTs), and platelet-activating factor (PAF).[1,2] Inhibition of this enzyme is thus envisaged to be a powerful way to lower the production of many important downstream inflammatory mediators with a single therapeutic agent. An inhibitor of $cPLA_2\alpha$ would be a novel therapeutic for the treatment of arthritis, pain, asthma, multiple sclerosis, stroke, atherosclerosis, or other diseases where these mediators play a role.[3]

We have recently discovered a class of potent and selective indole-based $cPLA_2\alpha$ inhibitors containing three pharmacophores, i.e., N_1-benzhydryl, C_2-primary sulfonamide, and C_3-linked benzoic acid such as compounds **1**−**5** in Figure 1.[4c] The compounds in Figure 1 are potent in isolated enzyme and whole blood assays but have high calculated $plogD_{7.4}$ of 7−9. Other previously reported Wyeth inhibitors [4a−e] and the only other class of compounds with activity in blood reported by Shionogi[5] have similarly high $plogD_{7.4}$ values.

The tendency to select for a lipophilic inhibitor is consistent with the fact that $cPLA_2\alpha$ works at the membrane−cytosol interface and binds arachidonyl glycerol phospholipid (**6**, MW 768.1, $plogD_{7.4} = 10.44$) as one of its natural substrates (Figure 2) in a deep active site.[6] In accord with Lipinski's "rule of five" guideline,[7] our highly lipophilic, high molecular weight inhibitors have shown low oral bioavailability in standard formulations.[4a−c] In the work reported here, our overall goal was to improve the bioavailability of these compounds. Since those inhibitors have comparable potency in both enzymatic and RWB assays, cell permeability is not a concern. We hypothesized that increased solubility might lead to higher exposure, and *we focused our medicinal chemistry efforts on the synthesis of analogues with lower lipophilicity.* Throughout this effort, we hoped to maintain the in vitro potency of these $cPLA_2\alpha$ inhibitors. Introduction of heteroatoms into the inhibitors was the route taken for this effort of lowering lipophilicity, and the region most amenable to heteroatom incorporation appeared to be the C_2 sulfonamide.[4a−c]

Chemistry

The most common approach to prepare sulfonamides is a direct coupling of an amine with a sulfonyl chloride. In our published work,[4a−c] we employed commercially available sulfonyl chlorides or prepared them from the corresponding alkyl halides by formation of the sulfonate followed by chlorination.[4a,8] However, these methods are of limited use for the work reported here, since most commercial sulfonyl chlorides and alkyl halides are hydrocarbon-based and few contain heteroatoms, especially nitrogens. In addition, preparing sulfonyl chlorides individually can be tedious and hazardous because of the corrosive nature of chlorinating reagents such as chlorine gas, oxalyl chloride, or thionyl chloride.

An alternative approach of making sulfonamide analogues entails reactions of nucleophiles with sulfonamides containing electrophilic centers, i.e., electrophilic sulfonamides, such as **9**−**12** in Scheme 1. This approach allows various heteroatom-bearing nucleophiles to be introduced directly to a late stage intermediate. The use of activated sulfonamides would assuage the need to protect the sulfonamide NH, one of our key pharmacophores.[4c] A survey of the literature revealed that reactions of chloromethanesulfonamides containing an unprotected NH, such as **8**, with heteroatom nucleophiles typically result in ring formation.[9]

[||] Dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday.

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[a] Abbreviations: $cPLA_2\alpha$, cytosolic phospholipase $A_2\alpha$; GLU, 7-hydroxycoumarinyl γ-linolenate; RWB, rat whole blood; HWB, human whole blood; PG, prostaglandin; LT, leukotriene; TX, thromboxane; PAF, platelet-activating factor; CPE, carrageenan paw edema; ESI, electrospray ionization; LC−MS, liquid chromatography−mass spectroscopy; AA, arachidonic acid.

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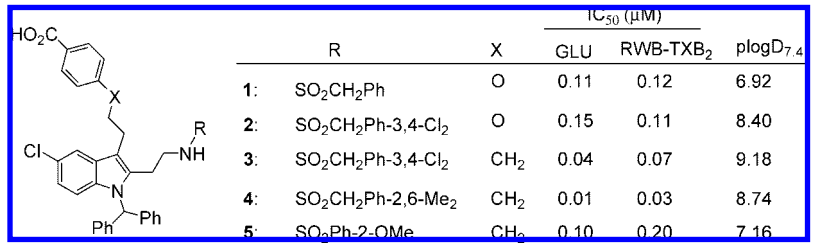


	R	X	IC_{50} (μM) GLU	IC_{50} (μM) RWB-TXB_2	$plogD_{7.4}$
1:	SO_2CH_2Ph	O	0.11	0.12	6.92
2:	SO_2CH_2Ph-3,4-Cl_2	O	0.15	0.11	8.40
3:	SO_2CH_2Ph-3,4-Cl_2	CH_2	0.04	0.07	9.18
4:	SO_2CH_2Ph-2,6-Me_2	CH_2	0.01	0.03	8.74
5:	SO_2Ph-2-OMe	CH_2	0.10	0.20	7.16

Figure 1. Wyeth $cPLA_2\alpha$ inhibitors.

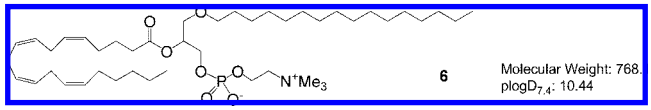


Figure 2. Representative natural substrate of $cPLA_2\alpha$.

Chloromethanesulfonamide **9** was prepared by the reaction of indole amine **7**[4c] with chloromethanesulfonyl chloride (Scheme 1). Reactions of chloromethanesulfonamide **9** with nitrogen, oxygen, and sulfur nucleophiles were scanned. When treated with morpholine, **9** reverted to indole amine **7**, which might result from cleavage of the sulfonamide product (Scheme 2) as suggested in the literature with related compounds.[10]

Reaction of chloromethanesulfonamide **9** with phenol gave a complex mixture from which a minor component was identified as the desired product by LC−MS. On the other hand, reactions of **9** with an array of substituted thiophenols went smoothly to provide thioethers (Scheme 3). Oxidation of thioether **24** using mCPBA resulted in the corresponding sulfoxide **25**, which after ester hydrolysis, afforded **38**, which has a significant lower $plogD_{7.4}$ than the thioether analogue **36** ($plogD_{7.4}$ for **36**/**38** = 9.3/7.2). Attempts to further oxidize **25** to the corresponding sulfone, however, led to decomposition. The desired product might not be stable under oxidative conditions, as has been reported with 1,3-dicarbonyl derivatives.[11] The vastly different reaction profiles among nitrogen, oxygen, and sulfur nucleophiles were quite intriguing. We postulate that the nitrogen and oxygen atoms of the respective nucleophilic addition products might have better σ^* overlap with the neighboring carbon compared to the corresponding sulfur, and this might contribute to their instability compared to the sulfur analogue.

Vinylsulfonamide **10** was prepared by the reaction of **7** with chloroethanesulfonyl chloride (Scheme 1). Michael reactions of vinylsulfonamide **10** with aromatic heterocycles in most cases progressed smoothly at elevated temperature without additional activators (Scheme 4). The reaction of **10** with 1*H*-tetrazole occurred after heating at 100 °C overnight to afford, after hydrolysis, two regioisomers, **83** and **84**. In contrast, reaction of **10** with 1*H*-1,2,3-triazole predominantly afforded **82**. The reaction of **10** with aliphatic amines was more efficient, as expected, and most reactions were facile at room temperature. In some cases, performing the reactions in refluxing 1-butanol was necessary to promote complete conversion.

Lastly, we incorporated small basic amines into the phenylmethanesulfonamide. Although Buchwald−Hartwig amination of aryl bromide has been widely used,[12] the resulting aniline analogues would not be basic enough to lower plogD. Therefore, our strategy was to prepare aldehyde **12** and subsequently perform reductive amination reactions as depicted in Scheme 5. The synthesis of (2-formylphenyl)methanesulfonyl chloride **13** has been reported;[13] to our knowledge, there are no reports in the literature of its reaction with amines. We speculated that the reaction of amine **8** and sulfonyl chloride **13** might lead to Schiff base formation rather than formation of the desired sulfonamide **11**. *We found, however, that by performance of the reaction in a biphasic system, Schiff base formation was deterred, and we were able to demonstrate the first synthetic application of this important and versatile (2-formylphenyl)-methanesulfonyl chloride* **13**.

Results and Discussion

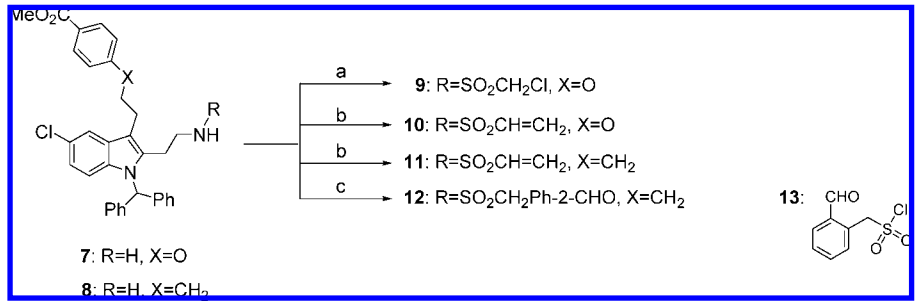
The assays used to characterize the inhibitors have been previously described.[4b,c] Briefly, the GLU micelle uses purified human $cPLA_2\alpha$ with the substrate 7-hydroxycoumarinyl-γ-linolenate (GLU) presented in a micelle containing a high concentration of detergent and lipid to limit artifacts due to disruption of the membrane interface by compounds that could inhibit without directly interacting with $cPLA_2\alpha$. The rat whole blood (RWB) assay monitors thromboxane production, which is dependent on $cPLA_2\alpha$ to release arachidonic acid, which is then processed by the COX-1 pathway. This assay requires that the inhibitors are membrane permeable to reach $cPLA_2\alpha$ in the cytosol and still active in the presence of serum albumin. Additional supporting assays are the human whole blood (HWB) assay and the murine MC-9 mast cell assay, which provide additional information on possible species selectivity, cellular permeability, and the effect of serum albumin binding.

Thioether Series. All of the sulfonamide analogues we synthesized were evaluated in the GLU and RWB assays.[4b,c] In general, the thioether derivatives gave good correlation between these assays. The introduction of thioether linkage was tolerated, since **26** compared favorably in potency with the phenethyl analogue **75**.[4c] Compound **31** emerged as the most potent inhibitor in this series, with whole blood activity comparable to that of lead compound **4** (Table 1). In contrast to the phenylmethanesulfonamide series,[4a−c] monosubstitution at the 2-position (**27**, **28**) did not improve in vitro activity. Furthermore, 2,6-disubstitution (**29**, **33**), found previously to lead to potent analogues,[4a] instead led to a 2- to 3-fold decrease in activity in both assays.

We next examined the effect of different oxidation states of the sulfur on activity. By comparison of thioether **36** and the corresponding sulfoxide **38** (Table 1), the GLU activity of **38** was essentially unchanged, while the RWB activity decreased by 4-fold. The sulfoxide was also marginally less potent in the MC-9 cellular assay (Table 6) and HWB (data not shown). Thus, the modest improvement in $plogD_{7.4}$ was offset by the apparent loss in cellular activity. The sulfonylsulfonamide **40**, with a remarkably low $plogD_{7.4}$ value of 4.5, was well tolerated.

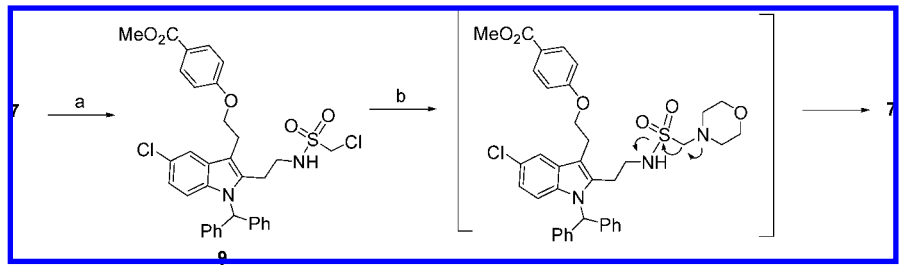
Nitrogen Series. Introduction of basic nitrogen atoms is an effective means to lower the lipophilicity of an inhibitor. Indeed, we observed that reactions of **10** with various nitrogen-containing heteroaromatics and subsequent hydrolysis of the esters afforded new analogues with $plogD_{7.4}$ up to 3 log units lower than that of **75** (Table 2). Interestingly, the GLU activities for this series were all quite similar, ranging from 0.32 to 0.76

Scheme 1. Synthesis of Electrophilic Sulfonamides[a]



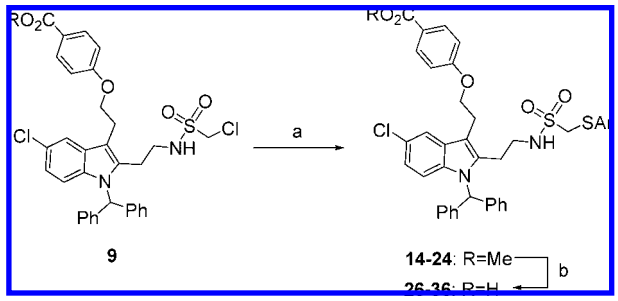
[a] Reagents: (a) $ClSO_2CH_2Cl$, DCM/$NaHCO_3$/H_2O; (b) $ClSO_2CH_2CH_2Cl$, Et_3N, THF; (c) **13**, DCM/$NaHCO_3$/H_2O.

Scheme 2. Reaction of **9** with Morpholine[a]



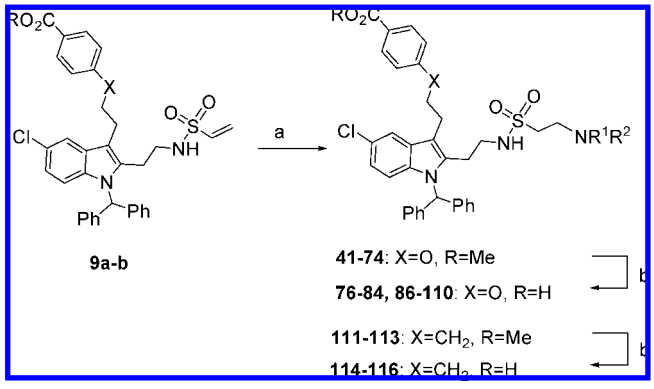
[a] Reagents: (a) $ClSO_2CH_2Cl$, DCM/$NaHCO_3$/H_2O; (b) morpholine, K_2CO_3, MeCN.

Scheme 3. Synthesis of Thioether Analogues **26**−**36**[a]



[a] Reagents: (a) ArSH, K_2CO_3, MeCN; (b) NaOH, MeOH, THF.

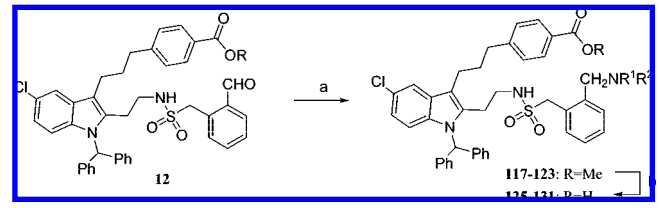
Scheme 4. Addition of Nitrogen Nucleophiles to Vinylsulfonamides **10** and **11**[a]



[a] Reagents: (a) HNR^1R^2, BuOH; (b) NaOH, MeOH, THF.

μM, despite varied numbers of heteroatoms (two to four) introduced. The two tetrazole analogues **83** and **84** demonstrate how regioisomers can have dramatic differences in activity. Despite similar potency in the cell free assay, **83** and **84** differed 12-fold in their RWB activities. Similarly, the HWB IC_{50} of **83** is ~2.0 μM, whereas **84** gives <25% inhibition at 10 μM and

Scheme 5. Introduction of Nitrogen Nucleophiles by Reductive Amination of **12**[a]

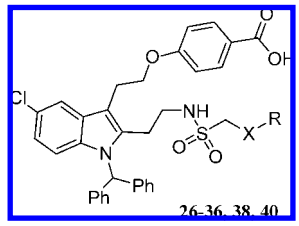


[a] Reagents: (a) HNR^1R^2, $NaBH(OAc)_3$, DCE; (b) NaOH, MeOH, THF.

84 is essentially inactive in the MC-9 cellular assay, which suggests the drop in potency is due to loss of cellular activity. Sulfonamide **76** is an example of a compound with nanomolar potency in the RWB assay and a $plogD_{7.4}$ of 4.65.

Reactions of aliphatic amines with compound **10** were also examined (Table 3). In general, the piperidine analogues were more potent than the corresponding pyrrolidine counterparts in the RWB assay. Since the former also have slightly higher $plogD_{7.4}$ values, this might indicate that better activities were conferred by higher lipophilicity, a reflection of the natural substrate. We observed that in pyrrolidine, piperidine, and morpholine derivatives, a 2-alkyl group on the heterocycles improved the activity in both assays. The 2-methyl (**87** and **103**) and 2,6-dimethyl (**90** and **104**) piperidine and pyrrolidine analogues were among the most active inhibitors, although they also had relatively high $plogD_{7.4}$ values. Of the three methylpiperidine isomers, the 2-methyl derivative (**87**) was more potent than the corresponding 3- and 4-counterparts (**88** and **89**, respectively). The existence of polar groups such as hydroxyl, carboxamide, or thiocarboxamide on the heterocycles appeared to reduce the potency in both assays as exemplified by **92** vs **89**, **98** vs **87**, and **109** vs **103**. The effect was more pronounced in the RWB in the five-membered heterocycles such as **109** and **110** where the carboxamide or thiocarboxamide group was adjacent to the linking nitrogen. The diminished level of activity seen in the RWB was also seen in the HWB assay and in the

Table 1. Thioether Analogues



compd	X	R	IC_{50} (μM) GLU[a]	IC_{50} (μM) RWB TXB_2[b]	$plogD_{7.4}$
1		Ph	0.11	0.12	6.9
2		3,4-Cl_2 Ph	0.15	0.11	8.4
75	CH_2	Ph	0.50	0.63	7.4
26	S	Ph	0.19	0.075	7.9
27	S	2-Cl Ph	0.15	0.090	8.6
28	S	2-Me Ph	0.15	0.080	8.4
29	S	2,6-Me_2 Ph	0.33	0.30	8.9
30	S	2,5-$(OMe)_2$ Ph	0.33	0.24	8.0
31	S	2,4-F_2 Ph	0.14	0.030	8.3
32	S	2,4-Cl_2 Ph	0.30	0.080	9.3
33	S	2,6-Cl_2 Ph	0.60	0.16	9.3
34	S	3,5-Cl_2 Ph	0.20	0.14	9.3
35	S	3-Cl-4-F Ph	0.17	0.070	8.8
36	S	3,4-Cl_2 Ph	0.24	0.14	9.3
38	S=O	3,4-Cl_2 Ph	0.18	0.56	7.2
40	SO_2	Me	0.15	0.48	4.5

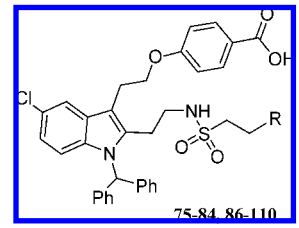
[a] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays.

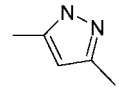
MC-9 cellular assay. Compounds **80**, **84**, and **109** have the largest shift in IC_{50} between our enzymatic and whole blood assays among the hundreds of compounds prepared for this program. It is noteworthy that compounds **110** and **95**, with $plogD_{7.4}$ of less than 4, had IC_{50} of ~1 μM in the GLU but much higher RWB activities. On the other hand, some modifications to introduce more heteroatoms or heterocycles were tolerated, such as **91** and **94**, although these did not lower the $plogD_{7.4}$ to the same extent. Remarkably, **93** is of comparable potency to compound **2**, and yet it has a $plogD_{7.4}$ of 4.3, 4 log units lower than **2**. This demonstrates that it is possible to modify the sulfonamide region of these compounds to greatly reduce the lipophilicity of the $cPLA_2\alpha$ inhibitors while maintaining the in vitro activity.

Next, the effect of the C_3 linker was examined. Selected pairs of heterocycles at C_2 were prepared with different linker atoms at the benzoic acid moiety (Table 4). In agreement with the SAR we reported earlier,[4a] it was found that our inhibitors with the all-carbon linker at C_3 consistently give better activities in both assays. This increase in potency might be reflective of the higher $plogD_{7.4}$ values of derivatives bearing the all-carbon linker compared to the ether-linked analogues: typically, the $plogD_{7.4}$ values differ by 1 log unit.

(2-Formylphenyl)methanesulfonamide Series. Although we had succeeded in lowering the lipophilicity of our $cPLA_2\alpha$ inhibitors synthesized via the Michael reaction strategy, potency remained a hurdle. Since ortho substitution of the phenylmethanesulfonamide moiety had a positive impact on potency,[4a] we sought to further explore this area. All of the new analogues, compared to their 2-methyl counterpart, **124**,[4a] have lower $plogD_{7.4}$ as well as comparable or improved activity in the GLU and comparable or slightly inferior activity in the RWB assay (Table 5). Compound **129** emerged as the most potent inhibitor

Table 2. Heteroaryl Analogues



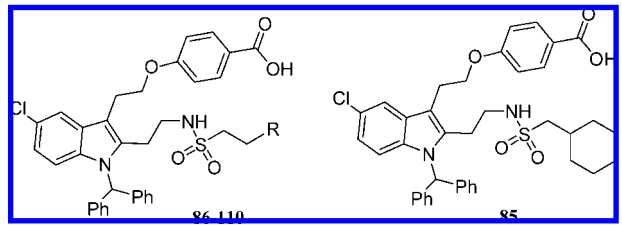
Compd	R	IC_{50} (μM) GLU[a]	IC_{50} (μM) RWB TXB_2[b]	$plogD_{7.4}$
75	Ph	0.50	0.63	7.40
76		0.32	0.54	4.65
77		0.51	0.20	5.15
78		0.76	0.28	5.16
79		0.45	0.16	5.64
80		0.55	5.8	5.82
81		0.41	1.5	4.12
82		0.50	2.0	4.92
83		0.38	0.45	5.6
84		0.47	5.6	5.8

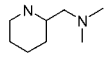
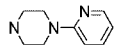
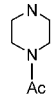
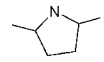
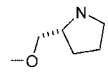
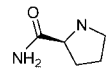
[a] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays.

in GLU in this series but suffered a 5-fold loss in RWB. Similarly, compound **130**, with a $plogD_{7.4}$ of 3.95, was potent in GLU but lost more activity than expected in the RWB assay. In general, the measured IC_{50} values in HWB are higher than that seen in RWB. This could be because a higher concentration of calcium ionophore A23187 is used to give reproducible stimulation of blood in humans. Interestingly, **128**−**131** were all essentially equipotent in RWB and HWB (data not shown), indicating that these compounds could have better potency in humans than predicted preclinically.

MC-9 Assay Data.[4b,c] In order to evaluate whether the new inhibitors prepared in this work are acting on $cPLA_2\alpha$ intracellularly, compounds were subjected to the MC-9 assay[4b,c] (Table 6). In this murine mast cell-like cell line, cross-linking of the IgE receptor with antigen activates $cPLA_2\alpha$, resulting in the release of AA, which is converted into both PGs via the

Table 3. Aliphatic Amine Analogues



Compd	R	IC_{50} (μM) GLU[a]	IC_{50} (μM) RWB TXB_2[b]	$plogD_{7.4}$
85	--	0.20	0.15	8.01
86		0.36	0.14	8.06
87		0.12	0.057	7.8
88		0.35	0.20	7.89
89		0.22	0.20	8.58
90		0.25	0.10	9.1
91		0.17	0.18	7.96
92		0.35	1.3	7.1
93		0.27	0.15	4.3
94		0.29	0.21	8.02
95		0.60	>10	3.38
96		0.27	1.2	7.29
97		0.49	0.24	6.26
98		0.20	0.48	5.11
99		0.39	0.53	6.95
100		0.25	0.40	7.06
101		0.45	0.34	7.98
102		0.35	0.33	7.58
103		0.22	0.077	8.1
104		0.13	0.074	8.58
105		0.33	0.32	6.9
106		0.70	0.31	6.6
107		NT	>1.25	4.58
108		0.25	0.33	8.07
109		0.35	3.2	6.1
110		0.75	5.0	3.96

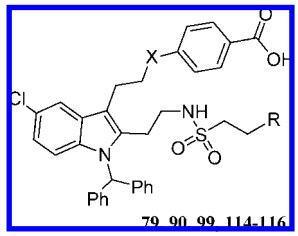
[a] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays.

COX-1 pathway and LTs via the 5-LO pathway. Addition of exogenous AA will bypass cPLA$_2$α and be processed by the COX-1 pathway to generate PGF$_2$α. Thus, *N*-[1-(1-benzothien-2-yl)ethyl]-*N*-hydroxyurea (zileuton),[14] a 5-LO inhibitor, blocks only LTB$_4$ production, while (2*S*)-2-(6-methoxy-2-naphthyl)-propanoic acid (naproxen), an inhibitor of COX-1 and -2, and (5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazole) **132** (SC-560),[15] a COX-1 inhibitor, block PGF$_2$α from both IgE stimulation and exogenously added AA. 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzene-sulfonamide (celecoxib)[16] is also active despite being a selective COX-2 inhibitor because at this concentration it inhibits COX-1. The cPLA$_2$α inhibitors block both PG and LT production upon IgE cross-linking and are inactive with addition of exogenous AA, thus demonstrating selective inhibition of cPLA$_2$α versus COX-1 and -2. Data from representative compounds of the thioether (**31**, **36**, **38**, **40**), heteroaryl (**79**, **83**, **84**), and aliphatic amine (**87**, **93**, **103**, **104**) series are presented.

As noted above, the MC-9 assay was also used to interpret poor RWB activity for compounds that were active in cell-free assays. For example, compounds **84** and **109** are poorly active in both RWB and MC-9 assays, suggesting that the loss in RWB potency is due to poor cellular permeability and not to an increase in serum binding.

Rat Carrageenan Paw Edema (CPE) Model.[17] Three of the aliphatic amine analogues and compound **3** were tested in the rat CPE model,[14] an acute inflammation model, and were

Table 4. Effect of C-3 Linkers on Potency and plogD$_{7.4}$

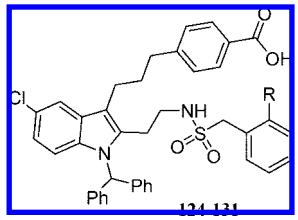


79, 90, 99, 114-116

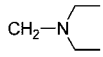
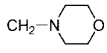
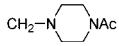
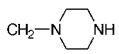
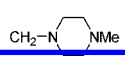
Compd	X	R	IC$_{50}$ (μM) GLU[a]	IC$_{50}$ (μM) RWB TXB$_2$[b]	plogD$_{7.4}$
79	O		0.45	0.16	5.64
114	CH_2		0.30	0.11	6.4
99	O		0.39	0.53	6.95
115	CH_2		0.20	0.14	7.8
90	O		0.25	0.10	9.1
116	CH_2		0.10	0.050	9.9

[a] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays.

Table 5. Sulfonamide Analogues with Basic Amines



124-131

Compd	R	IC$_{50}$ (μM) GLU[a]	IC$_{50}$ (μM) RWB TXB$_2$[b]	plogD$_{7.4}$
124	CH_3	0.026	0.025	8.22
125	CHO	0.020	0.050	7.14
126		0.030	0.037	7.81
127	CH_2OH	0.022	0.028	6.55
128		0.010	0.020	7.80
129		0.006	0.034	7.22
130		0.013	0.17	3.95
131		0.020	0.080	6.27

[a] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from duplicate assays. [b] Assay protocol reported previously;[4b,c] values are generated from at least two runs, and each run consists of a mean value generated from triplicate assays.

Table 6. MC-9 Assay Data for Selected Compounds[a]

compd	% inhibition @ μM inhibitor[b] LTB$_4$	PGF$_{2\alpha}$	PGF$_{2\alpha}$ AA feed
40	100 @ 0.5	100 @ 0.5	−47 @ 0.5
38	55 @ 0.11	45 @ 0.11	1.4 @ 1.0
36	64 @ 0.037	48 @ 0.037	33 @ 1.0
31	94 @ 0.037	77 @ 0.037	47 @ 1.0
79	89 @ 0.11	83 @ 0.11	5 @ 1.0
83	80 @ 0.333	71 @ 0.33	4 @ 1.0
84	59 @ 1.0	19 @ 1.0	−5 @ 1.0
87	62 @ 0.037	45 @ 0.037	14 @ 1.0
91	76 @ 0.11	66 @ 0.11	6 @ 1.0
93	62 @ 0.11	56 @ 0.11	13 @ 1.0
104	80 @ 0.11	69 @ 0.11	−2 @ 1.0
109	41 @ 0.33	41 @ 0.33	8 @ 1.0
115	69 @ 0.11	71 @ 0.11	9 @ 1.0
zileuton	50 @ 0.55	not active	not active
132	not active	79 @ 0.0005	79 @ 0.0005
celecoxib	not active	50 @ 0.40	50 @ 0.30
naproxen	not active	50 @ 0.20	50 @ 0.33

[a] Assay protocol reported previously.[4b,c] [b] Most compounds were assayed at 0.037, 0.11, 0.33, and 1 μM, and the % inhibition at the concentration that gave >50% inhibition is reported.

Table 7. Rat CPE Data for Selected Compounds[a]

compd	dose (mg/kg)	% inhibition of edema	plasma concn[b] (ng/mL)	SD	plasma concn[b] (μM)
naproxen	10	50			
3	15	51	3970	1000	5.3
91[c]	15	27.9	193.6	80.1	0.270
104[d]	15	37.0	165.6	10.7	0.232
115[d]	15	23.5	114.2	15.8	0.163

[a] Assay protocol reported previously.[4b,c] [b] End bleed concentration with iv dosing using 50/50 PEG/DMSO formulation; mean values from five mice. [c] Data derived from one single dose, with 10 mice per group. [d] Data derived from one dose response experiment for each compound, with 10 mice per group.

compared to naproxen, which was used to determine the maximum % inhibition (Table 7). These analogues and **3** have similar potency in rat whole blood. cPLA$_2\alpha$ inhibitors were dosed at 15 mg/kg iv, and the plasma concentration and inhibition of paw edema was determined 3 h later. All compounds were effective, but **3** and naproxen inhibited paw swelling by 50%, which is the maximal response generally seen. The superior activity of **3** can be attributed to the significantly higher level of exposure.

Summary. We have demonstrated the utility of electrophilic sulfonamides **9**−**12** as efficient and versatile intermediates in the preparation of cPLA$_2\alpha$ inhibitors with lower lipophilicity. Thiophenols have been added to chloromethanesulfonamide **9** to prepare thioether analogues and a corresponding sulfoxide. Various aromatic heterocycles and aliphatic amines have been added to vinylsulfonamide **10** in Michael fashion to provide new inhibitors with lower lipophilicity. We have shown that it is possible to retain comparable RWB activity and lower the lipophilicity by 3−4 orders of magnitude (e.g., compounds **77**, **78**, **93**, and **130**). Polar substituents such as hydroxyl, carboxamide, or thiocarboxamide had a negative impact on the RWB activity. Low molecular weight amines have been reacted with formyl derivative **12** to lead to new analogues with lower lipophilicity and good potency in both assays. There appears to be a fine balance between plogD$_{7.4}$ and in vitro activity. Overall, we have demonstrated the utility of electrophilic sulfonamides in the preparation of cPLA$_2\alpha$ inhibitors with reduced lipophilicity. The SAR in the cell free and RWB assays diverged for a small subset of compounds, but the MC-9 assay and HWB assays suggested that these compounds were not cell permeable. The aliphatic amine analogues were efficacious in

the rat CPE model at 15 mg/kg iv, but the efficacy was not as robust as past compounds because of lower plasma concentrations. Multiple examples of compounds with significantly lower plogD$_{7.4}$ that maintained nanomolar potency in the RWB assay were discovered in this effort. Compounds **77**, **78**, **93**, and **130** are among the most polar cPLA$_2\alpha$ inhibitors to have ever demonstrated this level of potency in a whole blood assay.

Experimental Section

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

Procedure for Chloromethylsulfonamide Formation. Methyl 4-{2-[1-Benzhydryl-5-chloro-2-(2-{[(chloromethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (9). To a solution of methyl 4-{2-[2-(2-aminoethyl)-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate[4c] **7** (304 mg, 0.564 mmol) in DCM (3.6 mL) were added chloromethanesulfonyl chloride (92 mg, 0.62 mmol) and saturated $NaHCO_3$ (1.8 mL). The reaction mixture was stirred at room temperature overnight followed by extractive workup to give the crude product (367 mg), a white foam, which was used without further purification.

Representative Procedure for Vinylsulfonamide Synthesis (10 and 11). Methyl 4-[2-(5-Chloro-1-(diphenylmethyl)-2-{2-[(vinylsulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (10). To a solution of **7**[4c] (330 mg, 0.612 mmol) in THF (4 mL) were added Et_3N (0.196 mL, 1.41 mmol) and 2-chloroethanesulfonyl chloride (0.072 mL, 0.73 mmol). The reaction mixture was allowed to stir at room temperature for 4 h followed by extractive workup and column chromatography using EtOAc/hexanes (30−35%) to give 262 mg (68%) of the title product as a solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 3.12−3.22 (m, 2 H), 3.24−3.35 (m, 4 H), 3.82 (s, 3 H), 4.34 (t, J = 6.7 Hz, 2 H), 5.85 (d, J = 10.2 Hz, 1 H), 5.98 (d, J = 16.5 Hz, 1 H), 6.49−6.55 (m, 1 H), 6.58 (d, J = 9.3 Hz, 1 H), 6.79 (dd, J = 8.8, 2.2 Hz, 1 H), 7.01 (d, J = 9.1 Hz, 2 H), 7.14−7.20 (m, 5 H), 7.32−7.40 (m, 6 H), 7.69 (d, J = 1.6 Hz, 1 H), 7.92 (d, J = 8.8 Hz, 2 H).

Methyl 4-[3-(5-Chloro-1-(diphenylmethyl)-2-{2-[(vinylsulfonyl)amino]ethyl}-1*H*-indol-3-yl)propyl]benzoate (11). Compound **11** was prepared from **8**[4a] in a similar manner to **10** in 63% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.93−2.02 (m, 2 H), 2.78−2.90 (m, 4 H), 3.03−3.21 (m, J = 20.9, 7.1 Hz, 4 H), 3.86 (s, 3 H), 5.86 (d, J = 10.2 Hz, 1 H), 5.91−6.04 (m, 1 H), 6.44 (s, 1 H), 6.48−6.61 (m, 2 H), 6.76 (dd, J = 8.8, 1.9 Hz, 1 H), 7.12−7.20 (m, 5 H), 7.32−7.40 (m, 8 H), 7.49 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 8.2 Hz, 2 H).

Methyl 4-{3-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-formylbenzyl)-sulfonyl]amino}ethyl)-1*H*-indol-3-yl]propyl}benzoate (12). To a solution of methyl 4-{3-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]propyl}benzoate[4a] **8** (63 mg, 0.12 mmol) in DCM (1.4 mL) were added (2-formylphenyl)methanesulfonyl chloride[6] (**13**, 36 mg, 0.16 mmol) and saturated $NaHCO_3$ (1 mL), and the reaction mixture was allowed to stir at room temperature for 4 h followed by extractive workup. Purification by flash column chromatography using EtOAc/hexanes (20−35%) afforded 34 mg (40%) of sulfonamide **12**, a yellow solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.82−1.89 (m, 2 H), 2.62−2.74 (m, 6 H), 3.72 (s, 3 H), 4.75 (s, 2 H), 6.25 (t, J = 6.1 Hz, 1 H), 6.39 (d, J = 8.8 Hz, 1 H), 6.62 (dd, J = 8.8, 2.3 Hz, 1 H), 6.97 (s, 1 H), 6.98−7.04 (m, J = 7.5, 2.1 Hz, 4 H), 7.20−7.27 (m, 9 H), 7.34 (d, J = 2.3 Hz, 2 H), 7.39−7.48 (m, 2 H), 7.76−7.84 (m, 2 H), 10.10 (s, 1 H).

Representative Procedures. Procedure A: Thiophenol displacement. See synthesis of **14**; Procedure B: Ester hydrolysis, see synthesis of **26**; Procedure C: Michael addition, see synthesis of **99**; Procedure D: Reductive animation, see synthesis of **120**.

Procedure A: Thiophenol Displacement. Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[(phenylsulfanyl)methyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (14). A solution of compound **9** (96 mg, 0.147 mmol), PhSH (0.018 mL, 0.18 mmol), and K_2CO_3 (24.8 mg, 0.179 mmol) in acetonitrile (1.2 mL) was stirred overnight and then heated to reflux for 3 h. The reaction mixture was diluted with EtOAc, washed with cold NH_4Cl, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography (1% MeOH/DCM) to afford the thioether intermediate **14** (51 mg, 48%). ^{1}H NMR (300 MHz, acetone-d_6) δ 3.19−3.34 (m, 6 H), 3.83 (s, 3 H), 4.31 (t, J = 6.7 Hz, 2 H), 4.41 (s, 2 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.70 (t, J = 5.5 Hz, 1 H), 6.78 (dd, J = 8.8, 2.2 Hz, 1 H), 7.01 (d, J = 8.5 Hz, 2 H), 7.12−7.17 (m, 5 H), 7.21−7.30 (m, 3 H), 7.32−7.39 (m, 6 H), 7.45−7.54 (m, 2 H), 7.68 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2-chlorophenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (15). Reaction of **9** with 2-chlorothiophenol afforded **15** in 53% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94−3.03 (m, 2 H), 3.08−3.17 (m, 2 H), 3.22 (t, J = 6.6 Hz, 2 H), 3.88 (s, 3 H), 4.08 (s, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.55 (t, J = 6.0 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.80−6.88 (m, 3 H), 6.92 (s, 1 H), 7.08 (d, J = 3.8 Hz, 4 H), 7.13−7.20 (m, 2 H), 7.28−7.38 (m, 7 H), 7.49 (dd, J = 7.4, 1.9 Hz, 1 H), 7.55 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2-methylphenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (16). Reaction of **9** with 2-methylthiophenol afforded **16** in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.93 (q, J = 6.7 Hz, 2 H), 3.05−3.16 (m, 2 H), 3.20 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 4.01 (s, 2 H), 4.21 (t, J = 6.5 Hz, 2 H), 4.44 (t, J = 6.0 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.78−6.88 (m, 3 H), 6.91 (s, 1 H), 7.02−7.12 (m, 5 H), 7.12−7.18 (m, 2 H), 7.23−7.35 (m, 6 H), 7.39 (d, J = 7.4 Hz, 1 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 9.1 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,6-dimethylphenyl)-sulfanyl]methyl}sulfonyl)amino]ethyl}-1H-indol-3-yl)ethoxy]benzoate (17). Reaction of **9** with 2,6-dimethylthiophenol afforded **17** in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 6 H), 2.82−2.95 (m, 2 H), 3.09 (t, J = 7.6 Hz, 2 H), 3.20 (t, J = 6.9 Hz, 2 H), 3.88 (s, 3 H), 4.21 (t, J = 6.6 Hz, 2 H), 4.31 (t, J = 6.5 Hz, 1 H), 6.53 (d, J = 9.1 Hz, 1 H), 6.79−6.94 (m, 4 H), 7.01−7.16 (m, 7 H), 7.22−7.35 (m, 6 H), 7.55 (s, 1 H), 7.96 (d, J = 8.2 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,5-dimethoxyphenyl)-sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (18). Reaction of **9** with 2,5-dimethoxythiophenol afforded **18** in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87−3.01 (m, 2 H), 3.00−3.13 (m, 2 H), 3.19 (t, J = 6.6 Hz, 2 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 3.88 (s, 3 H), 4.06−4.15 (m, 2 H), 4.20 (t, J = 6.6 Hz, 2 H), 4.77 (t, J = 5.8 Hz, 1 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.68−6.93 (m, 7 H), 7.00−7.13 (m, 5 H), 7.23−7.37 (m, 5 H), 7.54 (s, 1 H), 7.95 (d, J = 8.5 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,4-difluorophenyl)-thio]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (19). Reaction of **9** with 2,4-difluorothiophenol afforded **19** in 27% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98−3.08 (m, 2 H), 3.10−3.28 (m, 4 H), 3.88 (s, 3 H), 3.91 (s, 2 H), 4.24 (t, J = 6.3 Hz, 2 H), 4.57 (t, J = 6.0 Hz, 1 H), 6.54 (d, J = 9.1 Hz, 1 H), 6.72−6.80 (m, 1 H), 6.81−6.90 (m, 4 H), 6.93 (s, 1 H), 7.09 (d, J = 3.6 Hz, 4 H), 7.32 (d, J = 3.0 Hz, 6 H), 7.40−7.50 (m, 1 H), 7.56 (s, 1 H), 7.95 (d, J = 9.1 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,4-dichlorophenyl)-sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (20). Reaction of **9** with 2,4-dichlorothiophenol afforded **20** in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96−3.30 (m, 6 H), 3.88 (d, J = 2.2 Hz, 3 H), 4.01 (d, J = 1.9 Hz, 2 H), 4.24 (t, J = 6.5 Hz, 2 H), 4.58 (t, J = 6.2 Hz, 1 H), 6.49−6.59 (m, 1 H), 6.80−6.89 (m, 3 H), 6.92 (s, 1 H), 7.04−7.16 (m, 5 H), 7.22−7.48 (m, 8 H), 7.52−7.59 (m, 1 H), 7.89−8.00 (m, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,6-dichlorophenyl)-sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (21). Reaction of **9** with 2,6-dichlorothiophenol afforded **21** in 16% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89−3.02 (m, 2 H), 3.09−3.20 (m, 2 H), 3.24 (t, J = 6.6 Hz, 2 H), 3.88 (d, J = 1.6 Hz, 3 H), 4.03 (s, 2 H), 4.23 (t, J = 6.5 Hz, 2 H), 4.92 (t, J = 6.2 Hz, 1 H), 6.54 (d, J = 9.1 Hz, 1 H), 6.79−6.95 (m, 4 H), 7.04−7.22 (m, 6 H), 7.23−7.43 (m, 7 H), 7.57 (d, J = 2.2 Hz, 1 H), 7.96 (dd, J = 9.1, 1.6 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3,5-dichlorophenyl)-sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (22). Reaction of **9** with 3,5-dichlorothiophenol afforded **22** in 40%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00−3.10 (m, 2 H), 3.13−3.27 (m, 4 H), 3.88 (s, 3 H), 4.01 (s, 2 H), 4.24 (t, J = 6.5 Hz, 2 H), 4.53 (t, J = 6.2 Hz, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 3 H), 6.94 (s, 1 H), 7.09 (d, J = 4.9 Hz, 4 H), 7.24−7.36 (m, 9 H), 7.55 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 9.1 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3-chloro-4-fluorophenyl)thio]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (23). Reaction of **9** with 3-chloro-4-fluorothiophenol afforded **23** in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95−3.09 (m, 2 H), 3.10−3.28 (m, 4 H), 3.88 (s, 3 H), 3.97 (s, 2 H), 3.99−4.05 (m, 1 H), 4.23 (t, J = 6.0 Hz, 2 H), 4.63 (t, J = 5.8 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.79−6.88 (m, 4 H), 6.93 (s, 1 H), 7.04−7.12 (m, 4 H), 7.12−7.16 (m, 1 H), 7.27−7.35 (m, 6 H), 7.49−7.58 (m, 1 H), 7.90−7.98 (m, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3,4-dichlorophenyl)-thio]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (24). Reaction of **9** with 3,4-dichlorothiophenol afforded **24** in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98−3.30 (m, 6 H), 3.88 (s, 3 H), 3.99 (s, 2 H), 4.24 (t, J = 6.5 Hz, 2 H), 4.54 (t, J = 5.9 Hz, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.85 (d, J = 9.1 Hz, 3 H), 6.94 (s, 1 H), 7.04−7.13 (m, 4 H), 7.21−7.38 (m, 8 H), 7.54 (dd, J = 8.7, 1.8 Hz, 2 H), 7.95 (d, J = 8.8 Hz, 2 H).

Methyl 4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3,4-dichlorophenyl)-sulfinyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (25). To a solution of methyl 4-[2-(1-benzhydryl-5-chloro-2-{2-[({[(3,4-dichlorophenyl)thio]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (150 mg, 0.19 mmol) in THF (1 mL) at −78 °C was added 3-chloroperoxybenzoic acid (47 mg, 77% max, 0.21 mmol) in THF (2 mL) dropwise, and the mixture was stirred at −78 °C for 90 min and room temperature for 2 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. The volatiles were removed and the residue was purified by flash column chromatography (30% EtOAc−hexanes) to give **25** (64 mg, 42%) along with unreacted starting material (32 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11−3.21 (m, 4 H), 3.24 (t, J = 6.6 Hz, 2 H), 3.83−4.00 (m, 5 H), 4.25 (t, J = 6.6 Hz, 2 H), 5.18−5.23 (m, 1 H), 6.49−6.53 (m, 1 H), 6.80−6.84 (m, 1 H), 6.84−6.89 (m, 2 H), 6.95 (s, 1 H), 7.06−7.12 (m, 4 H), 7.26−7.34 (m, 7 H), 7.54 (t, J = 2.5 Hz, 1 H), 7.55−7.60 (m, 1 H), 7.66 (t, J = 2.5 Hz, 1 H), 7.90−7.98 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[(methylsulfonyl)methyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (133). A mixture of methyl 4-{2-[2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl]ethoxy}benzoate (100 mg, 0.19 mmol), (methanesulfonyl)-methanesulfonyl chloride (46 mg, 0.24 mmol), pyridine (0.045 mL, 0.56 mmol), and CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h and then at 65 °C for 1 h. The mixture was cooled to room temperature, and saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (20−50% EtOAc/hexane) afforded **26** as a white foam (56 mg, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98−3.13 (m, 5 H), 3.13−3.30 (m, 4 H), 3.87 (s, 3 H), 4.17 (s, 2 H), 4.24 (t, J = 6.5 Hz, 2 H), 5.23−5.36 (m, 1 H), 6.54 (d, J = 9.1 Hz, 1 H), 6.78−6.90 (m, 3 H), 6.93 (s, 1 H), 7.09 (dd, J = 5.6, 3.4 Hz, 4 H), 7.28−7.39 (m, 5 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H).

Procedure D: Michael Addition. Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-morpholinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (63). A solution of **10** (70.0 mg, 0.111 mmol) and morpholine (0.100 mL, 1.14 mmol) in ethanol (1 mL) was stirred for 5 h. The solvent was evaporated and the residue was dissolved in EtOAc and washed with water and brine to give **63** (71 mg, 89%). ^{1}H NMR (300 MHz, acetone-d_6) δ 2.20−2.40 (m, 4 H), 2.64 (t, J = 7.1 Hz, 2 H), 3.01−3.15 (m, 2 H), 3.27−3.38 (m, 3 H), 3.41−3.58 (m, 4 H), 3.82 (s, 3 H), 4.34 (t, J = 6.7 Hz, 2 H), 6.29−6.40 (m, 1 H), 6.57 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 6.97−7.04 (m, 2 H), 7.13−7.24 (m, 5 H), 7.27−7.41 (m, 6 H), 7.69 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 9.1 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (41). Reaction of **10** with pyrazole afforded **41** in 90% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 2.95−3.05 (m, 2 H), 3.07−3.16 (m, 2 H), 3.26 (t, J = 6.6 Hz, 2 H), 3.38 (t, J = 6.7 Hz, 2 H), 3.86 (s, 3 H), 4.29 (t, J = 6.5 Hz, 2 H), 4.44 (t, J = 7.0 Hz, 2 H), 6.21 (t, J = 2.2 Hz, 1 H), 6.34 (t, J = 1.8 Hz, 1 H), 6.47 (d, J = 9.1 Hz, 1 H), 6.73 (dd, J = 8.9, 2.1 Hz, 1 H), 6.94 (d, J = 9.1 Hz, 2 H), 7.04−7.13 (m, 5 H), 7.27−7.34 (m, 6 H), 7.43 (d, J = 1.6 Hz, 1 H), 7.56 (dd, J = 17.2, 2.1 Hz, 2 H), 7.91 (d, J = 8.8 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3-methyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (42). Reaction of **10** with 3-methylpyrazole afforded **42** in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34−2.39 (m, 3 H), 2.72−2.91 (m, 2 H), 3.00−3.11 (m, 2 H), 3.14−3.24 (m, 2 H), 3.27−3.38 (m, 2 H), 3.84−3.91 (m, 3 H), 4.15−4.26 (m, 2 H), 4.39 (t, J = 5.1 Hz, 2 H), 4.50−4.67 (m, 1 H), 5.94 (d, J = 15.4 Hz, 1 H), 6.13 (s, 1 H), 6.50 (dd, J = 8.8, 1.9 Hz, 1 H), 6.76−6.92 (m, 4 H), 7.01−7.13 (m, 4 H), 7.25−7.36 (m, 5 H), 7.53 (d, J = 4.7 Hz, 2 H), 7.93−8.01 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-methyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (43). Reaction of **10** with 4-methylpyrazole afforded **43** in 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 3 H), 2.80−2.91 (m, 2 H), 3.06 (t, J = 7.1 Hz, 2 H), 3.21 (t, J = 6.5 Hz, 2 H), 3.32 (t, J = 5.9 Hz, 2 H), 3.88 (s, 3 H), 4.21 (t, J = 6.3 Hz, 2 H), 4.40 (t, J = 5.8 Hz, 2 H), 4.48−4.56 (m, 1 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.77−6.91 (m, 4 H), 7.01−7.15 (m, 4 H), 7.24−7.34 (m, 7 H), 7.48−7.57 (m, 2 H), 7.96 (d, J = 8.8 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (44). Reaction of **10** with 3,5-dimethylpyrazole afforded **44** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08−2.13 (m, 3 H), 2.15−2.22 (m, 3 H), 2.82−2.93 (m, 2 H), 3.03−3.13 (m, 2 H), 3.20 (t, J = 6.6 Hz, 2 H), 3.25−3.34 (m, 2 H), 3.85−3.90 (m, 3 H), 4.21 (t, J = 6.5 Hz, 2 H), 4.34 (t, J = 5.9 Hz, 1 H), 5.78 (s, 1 H), 6.45−6.53 (m, 1 H), 6.77−6.93 (m, 4 H), 7.07 (dd, J = 3.8, 1.6 Hz, 4 H), 7.22−7.34 (m, 7 H), 7.53 (s, 1 H), 7.92−7.99 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-imidazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (45). Reaction of **10** with imidazole afforded **45** in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85−2.98 (m, 2 H), 3.01−3.17 (m, 4 H), 3.20 (t, J = 6.5 Hz, 2 H), 3.86 (s, 3 H), 4.20 (q, J = 6.8 Hz, 4 H), 5.33 (t, J = 4.8 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.71−7.00 (m, 6 H), 7.01−7.12 (m, 4 H), 7.23−7.38 (m, 7 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-1,2,4-triazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (46). Reaction of **10** with 1,2,4-triazole afforded **46** in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84−2.97 (m, 2 H), 3.05−3.35 (m, 6 H), 3.87 (s, 3 H), 4.18−4.30 (m, 2 H), 4.43−4.54 (m, 2 H), 4.80 (s, 1 H), 6.47−6.59 (m, 1 H), 6.77−6.94 (m, 4 H), 7.07 (d, J = 2.5 Hz, 4 H), 7.21−7.38 (m, 6 H), 7.54 (s, 1 H), 7.82 (s, 1 H), 7.96 (d, J = 8.5 Hz, 2 H), 8.19 (s, 1 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-1,2,3-triazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (47). Reaction of **10** with 1*H*-1,2,3-triazole afforded **47** in 23% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (br s, 2 H), 3.07−3.16 (m, 2 H), 3.17−3.26 (m, 2 H), 3.30−3.39 (m, 2 H), 3.85 (s, 3 H), 4.17−4.28 (m, 2 H), 4.61−4.73 (m, 3 H), 6.48−6.57 (m, 1 H), 6.76−6.94 (m, 4 H), 7.07 (dd, J = 6.2, 2.9 Hz, 4 H), 7.23−7.36 (m, 5 H), 7.54 (t, J = 2.5 Hz, 2 H), 7.60−7.65 (m, 1 H), 7.90−7.99 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2*H*-tetrazol-2-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (48) and Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-tetrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (49). Reaction of **10** with 1*H*-tetrazole afforded **48** (41%) and **49** (52%). ^{1}H NMR for **48** (300 MHz, $CDCl_3$) δ 2.89 (q, J = 6.8 Hz, 2 H), 3.13 (t, J = 7.6 Hz, 2 H), 3.23 (t, J = 6.0 Hz, 2 H), 3.43 (t, J = 6.9 Hz, 2 H), 3.88 (s, 3 H), 4.25 (t, J = 6.3 Hz, 2 H), 4.39 (t, J = 5.9 Hz, 1 H), 4.93 (t, J = 6.9 Hz, 2 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.80−6.94 (m, 4 H), 7.03−7.11 (m, 4 H), 7.23−7.37 (m, 6 H), 7.55 (d, J = 1.6 Hz, 1 H), 7.96 (d, J = 9.1 Hz, 2 H), 8.38 (s, 1 H). ^{1}H NMR for **49** (300 MHz, $CDCl_3$) δ 2.88−2.99 (m, 2 H), 3.14 (t, J = 7.1 Hz, 2 H), 3.18−3.31 (m, 4 H), 3.87 (s, 3 H), 4.25 (t, J = 6.2 Hz, 2 H), 4.59 (t, J = 6.0 Hz, 1 H), 4.68 (t, J = 6.3 Hz, 2 H), 6.55 (d, J = 9.1 Hz, 1 H), 6.78−6.93 (m, 4 H), 7.01−7.17 (m, 4 H), 7.20−7.40 (m, 6 H), 7.55 (d, J = 1.6 Hz, 1 H), 7.87−8.05 (m, 2 H), 8.57 (s, 1 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1-piperidinyl)ethyl]-sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (50). Reaction of **10** with piperidine afforded **50** in 99% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.32−1.39 (m, 2 H), 1.41−1.53 (m, 4 H), 2.31−2.48 (m, 4 H), 2.64−2.78 (m, 2 H), 3.03−3.21 (m, 2 H), 3.25−3.38 (m, 6 H), 3.82 (s, 3 H), 4.34 (t, J = 6.7 Hz, 2 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.78 (dd, 1 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.13−7.24 (m, 5 H), 7.29−7.42 (m, 6 H), 7.69 (d, J = 2.2 Hz, 1 H), 7.92 (d, J = 8.8 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-methyl-1-piperidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (51). Reaction of **10** with 2-methylpiperidine afforded **51** in 91% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.95 (d, J = 6.3 Hz, 1 H), 1.09−1.38 (m, 4 H), 1.40−1.60 (m, 2 H), 1.95−2.03 (m, 1 H), 2.11−2.22 (m, 1 H), 2.62−2.78 (m, 2 H), 2.94−3.10 (m, 3 H), 3.24−3.37 (m, 6 H), 3.83 (s, 3 H), 4.34 (t, J = 6.6 Hz, 2 H), 6.35 (s, 1 H), 6.57 (d, J = 8.8 Hz, 2 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 7.01 (d, J = 8.8 Hz, 2 H), 7.08−7.25 (m, 5 H), 7.31−7.43 (m, 6 H), 7.69 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 9.1 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3-methylpiperidin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (52). Reaction of **10** with 3-methylpiperidine afforded **52** in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, J = 6.6 Hz, 3 H), 1.11−1.38 (m, 3 H), 1.45−1.61 (m, 4 H), 1.71−1.85 (m, 1 H), 2.59−2.76 (m, 4 H), 2.91−3.07 (m, 4 H), 3.16−3.29 (m, 4 H), 3.88 (s, 3 H), 4.23 (t, J = 6.6 Hz, 2 H), 5.72 (s, 1 H), 6.51 (d, J = 9.1 Hz, 1 H), 6.81 (dd, J = 8.8, 1.9 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.99 (s, 1 H), 7.05−7.14 (m, 4 H), 7.27−7.35 (m, 5 H), 7.55 (d, J = 2.2 Hz, 1 H), 7.92−7.99 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-methylpiperidin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (53). Reaction of **10** with 4-methylpiperidine afforded **53** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.6 Hz, 3 H), 0.86−1.01 (m, 2 H), 1.21−1.35 (m, 1 H), 1.28−1.35 (m, 1 H), 1.54 (d, J = 12.9 Hz, 2 H), 1.90 (t, J = 11.3 Hz, 2 H), 2.65−2.76 (m, 4 H), 2.96 (t, J = 6.2 Hz, 2 H), 3.00−3.08 (m, 2 H), 3.16−3.30 (m, 4 H), 3.88 (s, 3 H), 4.23 (t, J = 6.6 Hz, 2 H), 5.62 (s, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.9, 2.1 Hz, 1 H), 6.84−6.91 (m, 2 H), 6.98 (s, 1 H), 7.11 (dd, J = 3.6, 2.2 Hz, 4 H), 7.28−7.34 (m, 5 H), 7.55 (s, 1 H), 7.96 (d, J = 9.1 Hz, 2 H).

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[(2*R*,6*S*)-2,6-dimethyl-1-piperidinyl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (54). Reaction of **10** with *cis*-2,6-dimethylpiperidine afforded **54** in 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93−1.38 (m, J = 72.5 Hz, 12 H), 1.58 (d, J = 30.8 Hz, 2 H), 2.18 (s, 2 H), 2.86 (s, 2 H), 2.99−3.31 (m, 6 H), 3.88 (s, 3 H), 4.25 (t, J = 6.6 Hz, 2 H), 6.54 (d, J = 8.5 Hz, 1 H), 6.84 (t, J = 8.4 Hz, 3 H), 6.96 (s, 1 H), 7.09 (s, 4 H), 7.21−7.37 (m, 6 H), 7.55 (s, 1 H), 7.95 (d, J = 8.5 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-thiomorpholinyl)-ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (55). Reaction of **10** with thiomorpholine afforded **55** in 93% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.48−2.61 (m, 8 H), 2.69 (t, J = 7.1 Hz, 2 H), 3.03−3.12 (m, 2 H), 3.26−3.37 (m, 6 H), 3.83 (s, 3 H), 4.34 (t, J = 6.9 Hz, 2 H), 6.31 (br s, 1 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.14−7.22 (m, J = 7.4, 3.6 Hz, 5 H), 7.34−7.41 (m, 6 H), 7.69 (d, J = 1.6 Hz, 1 H), 7.93 (d, J = 9.1 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-hydroxy-1-piperidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (56). Reaction of **10** with 4-hydroxypiperidine afforded **56** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21−1.47 (m, 2 H), 1.66−1.87 (m, 2 H), 2.07−2.32 (m, 2 H), 2.72 (d, J = 39.0 Hz, 4 H), 2.95−3.11 (m, 4 H), 3.14−3.31 (m, 4 H), 3.64 (s, 1 H), 3.88 (s, 3 H), 4.24 (t, J = 6.5 Hz, 2 H), 5.45 (s, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.78−6.91 (m, 3 H), 6.99 (s, 1 H), 7.10 (d, J = 1.1 Hz, 4 H), 7.24−7.28 (m, 1 H), 7.28−7.36 (m, 6 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.92−8.00 (m, 2 H).

4-{2-[1-Benzhydryl-5-chloro-2-(2-{[(2-{2-[(dimethylamino)methyl]-1-piperidinyl}ethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoate (57). Reaction of **10** with *N*-(2-piperidylmethyl)dimethylamine afforded **57** in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08−1.45 (m, 3 H), 1.61 (s, 2 H), 1.80 (d, J = 4.1 Hz, 2 H), 2.02−2.34 (m, 7 H), 2.51−2.74 (m, 3 H), 2.74−3.06 (m, 7 H), 3.09−3.32 (m, 4 H), 3.88 (s, 3 H), 4.22 (t, J = 6.7 Hz, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.78 (d, J = 8.8 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.00 (s, 1 H), 7.12 (s, 4 H), 7.28 (d, J = 10.2 Hz, 6 H), 7.54 (s, 1 H), 7.96 (d, J = 8.2 Hz, 2 H).

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[4-(2-pyridinyl)-1-piperazinyl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (58). Reaction of **10** with 1-(2-pyridyl)piperazine afforded **58** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 4 H), 2.74−2.93 (m, 2 H), 3.03 (s, 4 H), 3.17−3.54 (m, J = 23.6 Hz, 4 H), 3.88 (s, 3 H), 3.89−4.00 (m, 1 H), 4.15−4.33 (m, 2 H), 5.19−5.28 (m, 1 H), 6.44−6.95 (m, 7 H), 6.97 (s, 1 H), 7.09 (d, J = 3.3 Hz, 4 H), 7.24−7.43 (m, 6 H), 7.44−7.62 (m, 1 H), 7.94 (d, J = 8.5 Hz, 2 H), 8.15−8.29 (m, 1 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(*cis*-3,5-dimethylpiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (59). Reaction of **10** with *cis*-2,6-dimethylpiperazine afforded **59** in 97% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.94 (d, J = 6.0 Hz, 6 H), 1.51−1.63 (m, J = 10.2, 10.2 Hz, 2 H), 2.61−2.69 (m, 4 H), 2.69−2.80 (m, 2 H), 3.09 (t, J = 6.9 Hz, 2 H), 3.25−3.35 (m, 6 H), 3.82 (s, 3 H), 4.34 (t, J = 6.6 Hz, 2 H), 6.35 (br s, 1 H), 6.56 (d, J = 8.8 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 7.02 (d, J = 9.1 Hz, 2 H), 7.14−7.23 (m, 5 H), 7.32−7.39 (m, 6 H), 7.69 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 9.1 Hz, 2 H).

4-(2-{2-[2-({[2-(4-Acetyl-*cis*-3,5-dimethylpiperazin-1-yl)ethyl]sulfonyl}-amino)ethyl]-1-benzhydryl-5-chloro-1*H*-indol-3-yl}ethoxy)benzoate (60). To a solution of **59** (31 mg, 0.042 mmol) in DCM (1 mL) were added Et_3N (0.1 mL, mmol) and Ac_2O (0.060 mL, mmol). The

reaction mixture was stirred at room temperature for 5 h followed by an extractive workup and silica gel chromatography (3.5% MeOH/$CHCl_3$) to give **60** (17.3 mg, 52%). ^{1}H NMR (300 MHz, acetone-d_6) δ 1.23 (d, J = 6.3 Hz, 6 H), 1.97−2.03 (m, 2 H), 2.00 (s, 3 H), 2.59−2.72 (m, 4 H), 2.83−2.89 (m, 2 H), 3.07−3.18 (m, 2 H), 3.28−3.37 (m, 6 H), 3.83 (s, 3 H), 4.34 (t, J = 6.7 Hz, 2 H), 6.42 (t, J = 4.8 Hz, 1 H), 6.57 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.15−7.22 (m, 5 H), 7.33−7.40 (m, 6 H), 7.69 (d, J = 2.2 Hz, 1 H), 7.92 (d, J = 9.1 Hz, 2 H).

4-(2-{2-[2-({[2-(4-Acetylpiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1-benzhydryl-5-chloro-1*H*-indol-3-yl}ethoxy)benzoate (61). Reaction of **10** with 1-acetylpiperazine afforded **61** in 91% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.95 (s, 3 H), 2.21−2.30 (m, 2 H), 2.30−2.36 (m, 2 H), 2.68 (t, J = 7.0 Hz, 2 H), 3.10 (t, J = 7.0 Hz, 2 H), 3.27−3.42 (m, 10 H), 3.82 (s, 3 H), 4.34 (t, J = 6.6 Hz, 2 H), 6.34 (br s, 1 H), 6.57 (d, J = 8.5 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 7.01 (d, J = 9.1 Hz, 2 H), 7.13−7.23 (m, 5 H), 7.29−7.41 (m, 6 H), 7.69 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 8.8 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-methyl-3-oxopiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (62). Reaction of **10** with 3-methyl-2-piperazinone afforded **62** in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27−1.31 (m, 3 H), 2.38−2.49 (m, 1 H), 2.79 (dd, J = 12.6, 5.3 Hz, 2 H), 2.89−3.10 (m, 6 H), 3.10−3.27 (m, 6 H), 3.87 (s, 3 H), 4.25 (t, J = 6.4 Hz, 2 H), 4.94 (t, J = 5.7 Hz, 1 H), 5.88 (s, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.82 (dd, J = 9.0, 2.1 Hz, 1 H), 6.84−6.90 (m, 2 H), 6.96 (s, 1 H), 7.10 (d, J = 2.8 Hz, 4 H), 7.28−7.35 (m, 6 H), 7.55 (d, J = 2.0 Hz, 1 H), 7.92−7.98 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (64). Reaction of **10** with (1*S*,4*S*)-(+)-2-aza-5-oxabicyclo[2,2,1]heptane afforded **64** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55−1.71 (m, 2 H), 2.41 (d, J = 10.9 Hz, 1 H), 2.64 (d, J = 7.8 Hz, 1 H), 2.88−3.11 (m, 6 H), 3.15−3.29 (m, 4 H), 3.37 (s, 1 H), 3.56 (dd, J = 8.2, 1.6 Hz, 1 H), 3.83 (d, J = 8.1 Hz, 1 H), 3.88 (s, 3 H), 4.24 (t, J = 6.7 Hz, 2 H), 4.29 (s, 1 H), 5.08 (br s, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.82 (dd, J = 8.8, 2.0 Hz, 1 H), 6.85−6.89 (m, 2 H), 6.97 (s, 1 H), 7.06−7.12 (m, 4 H), 7.28−7.35 (m, 6 H), 7.55 (d, J = 1.8 Hz, 1 H), 7.93−7.98 (m, 2 H).

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[(3*R*,5*S*)-3,5-dimethylmorpholin-4-yl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (65). Reaction of **10** with (3*R*,5*S*)-3,5-dimethylmorpholine afforded **65** in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.96 (m, 1 H), 1.08 (d, J = 6.3 Hz, 6 H), 1.28−1.38 (m, 1 H), 1.70 (t, J = 10.6 Hz, 2 H), 2.54 (d, J = 10.6 Hz, 2 H), 2.70 (t, J = 6.4 Hz, 2 H), 2.92−3.06 (m, 4 H), 3.17−3.28 (m, 4 H), 3.33−3.44 (m, 2 H), 3.88 (s, 3 H), 4.24 (t, J = 6.6 Hz, 2 H), 5.07 (t, J = 5.9 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.82 (dd, J = 8.8, 2.0 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.96 (s, 1 H), 7.09 (dd, J = 6.3, 2.8 Hz, 4 H), 7.28−7.35 (m, 6 H), 7.55 (d, J = 1.8 Hz, 1 H), 7.96 (d, J = 8.8 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1-pyrrolidinyl)ethyl]-sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (66). Reaction of **10** with pyrrolidine afforded **66** in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 4 H), 2.48 (s, 4 H), 2.90 (t, J = 6.0 Hz, 2 H), 2.95−3.12 (m, 4 H), 3.12−3.32 (m, 4 H), 3.88 (s, 3 H), 4.23 (t, J = 6.3 Hz, 2 H), 5.44 (s, 1 H), 6.52 (d, J = 9.1 Hz, 1 H), 6.75−6.91 (m, 3 H), 6.98 (s, 1 H), 7.10 (d, J = 1.1 Hz, 4 H), 7.22−7.40 (m, 6 H), 7.55 (d, J = 1.1 Hz, 1 H), 7.96 (d, J = 9.1 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-methyl-1-pyrrolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (67). Reaction of **10** with 2-methylpyrrolidine afforded **67** in 91% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.98 (d, J = 6.0 Hz, 3 H), 1.16−1.31 (m, 2 H), 1.54−1.64 (m, 2 H), 1.82−2.00 (m, 2 H), 2.19−2.32 (m, 1 H), 2.35−2.47 (m, 1 H), 2.90−3.00 (m, 1 H), 3.04−3.13 (m, 2 H), 3.24−3.37 (m, 6 H), 3.83 (s, 3 H), 4.34 (t, J = 6.7 Hz, 2 H), 6.30 (br s, 1 H), 6.57 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.8, 2.2 Hz, 1 H), 7.01 (d, J = 8.8 Hz, 2 H), 7.14−7.23 (m, 5 H), 7.31−7.40 (m, 6 H), 7.69 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 9.1 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2,5-dimethyl-1-pyrrolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (68). Reaction of **10** with 2,5-dimethylpyrrolidine afforded **68** in 81% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.96 (d, J = 6.0 Hz, 6 H), 1.16−1.29 (m, 2 H), 1.67−1.77 (m, 2 H), 2.45−2.55 (m, 2 H), 2.98 (s, 4 H), 3.19−3.38 (m, 6 H), 3.83 (s, 3 H), 4.34 (t, J = 6.7 Hz, 2 H), 6.41 (t, J = 6.0 Hz, 1 H), 6.57 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 6.97−7.04 (m, 2 H), 7.14−7.22 (m, 5 H), 7.33−7.41 (m, 6 H), 7.69 (d, J = 2.2 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1,3-thiazolidin-3-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (69). Reaction of **10** with thiazolidine afforded **69** in 33% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70−3.08 (m, 10 H), 3.12−3.28 (m, 4 H), 3.74−3.79 (m, 2 H), 3.88 (s, 3 H), 4.18−4.29 (m, 2 H), 4.83 (s, 1 H), 6.49−6.56 (m, 1 H), 6.77−6.89 (m, 3 H), 6.96 (s, 1 H), 7.05−7.14 (m, 4 H), 7.23−7.35 (m, 6 H), 7.55 (d, J = 1.9 Hz, 1 H), 7.92−7.99 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3-hydroxy-1-pyrrolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (70). Reaction of **10** with 3-pyrrolidinol afforded **70** in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23−1.29 (m, 1 H), 2.02−2.43 (m, 4 H), 2.71−2.90 (m, 2 H), 2.93−3.28 (m, 11 H), 3.88 (s, 3 H), 4.23 (t, J = 6.5 Hz, 2 H), 4.30 (s, 1 H), 6.50 (d, J = 9.1 Hz, 1 H), 6.76−6.83 (m, 1 H), 6.88 (dd, J = 8.9, 1.8 Hz, 2 H), 6.97 (s, 1 H), 7.06−7.14 (m, 4 H), 7.26 (d, J = 1.9 Hz, 2 H), 7.28−7.34 (m, 4 H), 7.55 (d, J = 1.9 Hz, 1 H), 7.96 (dd, J = 8.8, 1.9 Hz, 2 H).

4-{2-[5-Chloro-2-{2-[({2-[3-(dimethylamino)pyrrolidin-1-yl]ethyl}-sulfonyl)amino]ethyl}-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (71). Reaction of **10** with 3-(dimethylamino)pyrrolidine afforded **71** in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56−1.85 (m, 2 H), 2.16 (s, 6 H), 2.31−2.62 (m, 4 H), 2.62−2.72 (m, 1 H), 2.72−2.82 (m, 1 H), 2.83−2.91 (m, 1 H), 2.96 (q, J = 6.0 Hz, 2 H), 3.01−3.13 (m, 2 H), 3.15−3.31 (m, 4 H), 3.88 (s, 3 H), 4.23 (t, J = 6.6 Hz, 2 H), 5.30 (s, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.76−6.91 (m, 3 H), 6.99 (s, 1 H), 7.11 (d, J = 2.5 Hz, 4 H), 7.22−7.37 (m, 6 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.96 (d, J = 8.5 Hz, 2 H).

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoate (72). Reaction of **10** with (*S*)-(+)-2-(methoxymethyl)pyrrolidine afforded **72** in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38−1.84 (m, 5 H), 2.50−2.64 (m, 2 H), 2.75−3.35 (m, 14 H), 3.46 (dd, J = 10.0, 3.2 Hz, 1 H), 3.88 (s, 3 H), 4.23 (t, J = 6.9 Hz, 2 H), 6.37 (s, 1 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.79 (dd, J = 8.8, 2.0 Hz, 1 H), 6.84−6.91 (m, 2 H), 6.96−7.00 (m, 1 H), 7.06−7.16 (m, 4 H), 7.27−7.35 (m, 5 H), 7.55 (d, J = 2.3 Hz, 1 H), 7.91−7.99 (m, 2 H).

4-{2-[2-{2-[({2-[(2*S*)-2-(Aminocarbonyl)pyrrolidin-1-yl]ethyl}sulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoate (73). Reaction of **10** with L-prolinamide afforded **73** in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63−1.89 (m, 4 H), 2.06−2.21 (m, 2 H), 2.62−2.73 (m, 1 H), 2.79−2.90 (m, 1 H), 2.91−3.14 (m, 6 H), 3.14−3.29 (m, 4 H), 3.88 (s, 3 H), 4.24 (t, J = 6.6 Hz, 2 H), 5.42 (s, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.82 (dd, J = 8.8, 2.3 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.96 (s, 1 H), 7.04−7.13 (m, 4 H), 7.28−7.34 (m, 6 H), 7.55 (d, J = 2.0 Hz, 1 H), 7.92−7.98 (m, 2 H).

Methyl 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-thioxo-1-imidazolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoate (74). Reaction of **10** with 2-imidazolinethione afforded **74** in 17% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00−3.13 (m, 4 H), 3.15−3.29 (m, 4 H), 3.48−3.59 (m, 2 H), 3.62−3.73 (m, 2 H), 3.84−3.93 (m, 5 H), 4.20−4.29 (m, 2 H), 5.72 (s, 1 H), 5.77−5.85 (m, 1 H), 6.47−6.55 (m, 1 H), 6.77−6.84 (m, 1 H), 6.85−6.93 (m, 2 H), 6.97 (s, 1 H), 7.06−7.18 (m, 4 H), 7.23−7.38 (m, 6 H), 7.51−7.59 (m, 1 H), 7.89−8.01 (m, 2 H).

Methyl 4-(3-{1-Benzhydryl-5-chloro-2-[2-({[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoate (111). Reaction of **11** with 3,5-dimethylpyrazole afforded **111** in 100% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.00−2.06 (m,

2 H), 2.18 (s, 3 H), 2.20 (s, 3 H), 2.69−2.92 (m, 4 H), 3.08−3.16 (m, 4 H), 3.42 (t, J = 6.9 Hz, 2 H), 3.85 (s, 3 H), 4.31 (t, J = 6.9 Hz, 2 H), 5.81 (s, 1H), 6.42 (s, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.8, 2.2 Hz, 1 H), 7.08−7.20 (m, 5 H), 7.28−7.39 (m, 7 H), 7.60 (dd, J = 5.8, 3.3 Hz, 1 H), 7.77−7.85 (m, 1 H), 7.88−7.97 (m, 2 H).

Methyl 4-(3-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-morpholinyl)-ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoate (112). Reaction of **11** with morpholine afforded **112** in 100% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.93−2.03 (m, 2 H), 2.26−2.35 (m, 4 H), 2.65 (t, J = 7.1 Hz, 2 H), 2.69−2.75 (m, 2 H), 2.77−2.93 (m, 4 H), 3.08 (t, J = 7.0 Hz, 2 H), 3.44−3.55 (m, 6 H), 3.85 (s, 3 H), 6.31 (br s, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.76 (dd, J = 8.8, 2.2 Hz, 1 H), 7.14−7.22 (m, J = 4.9, 2.2 Hz, 5 H), 7.31−7.42 (m, 8 H), 7.50 (d, J = 2.2 Hz, 1 H), 7.92 (d, J = 8.2 Hz, 2 H).

Methyl 4-(3-{1-Benzhydryl-5-chloro-2-[2-({[2-(2,6-dimethyl-1-piperidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoate (113). Reaction of **11** with *cis*-2,6-dimethylpiperidine afforded **113** in 59% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.82 (s, 3 H), 0.85 (s, 3 H), 0.92−1.21 (m, 4 H), 1.30−1.49 (m, 2 H), 1.82−1.92 (m, 2 H), 1.97−2.11 (m, 2 H), 2.66−2.85 (m, 6 H), 2.91−3.10 (m, 4 H), 3.10−3.20 (m, 2 H), 3.74 (s, 3 H), 6.26 (t, J = 5.8 Hz, 1 H), 6.41 (d, J = 8.8 Hz, 1 H), 6.65 (dd, J = 8.9, 2.1 Hz, 1 H), 7.00−7.09 (m, 5 H), 7.18−7.30 (m, 8 H), 7.38 (d, J = 1.9 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H).

Representative Procedure for Reductive Amination. Methyl 4-(3-{5-Chloro-1-(diphenylmethyl)-2-[2-({[2-(morpholin-4-ylmethyl)-benzyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoate (120). To compound **12** (58 mg, 0.081 mmol) in DCE (2 mL) at 0 °C were added morpholine (0.0092 mL, 0.105 mmol) and $NaBH(OAc)_3$ (27 mg, 0.13 mmol), and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. Purification by flash column chromatography (35−50% EtOAc/hexanes) gave compound **120** as a white solid (41 mg, 64%). ^{1}H NMR (400 MHz, acetone-d_6) δ 1.82−1.89 (m, 4 H), 2.13−2.21 (m, 4 H), 2.61−2.74 (m, 6 H), 3.35−3.44 (m, 4 H), 3.48 (s, 2 H), 3.72 (s, 3 H), 4.51 (s, 2 H), 6.38 (d, J = 9.1 Hz, 1 H), 6.62 (dd, J = 8.8, 2.3 Hz, 1 H), 6.97 (s, 1 H), 7.01 (dd, J = 7.6, 2.0 Hz, 4 H), 7.03−7.07 (m, 1 H), 7.10−7.14 (m, 2 H), 7.15−7.19 (m, 1 H), 7.21−7.27 (m, 8 H), 7.34 (d, J = 2.3 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 2 H).

Methyl 4-{3-[5-Chloro-2-{2-[({2-[(diethylamino)methyl]benzyl}sulfonyl)amino]ethyl}-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (118) and Methyl 4-(3-{5-Chloro-1-(diphenylmethyl)-2-[2-({[2-(hydroxymethyl)benzyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoate (119). Compound **12** was reacted with $HNEt_2$ to afford **118** (41%) and **119** (15%), both as white solids. ^{1}H NMR for **118** (400 MHz, acetone-d_6) δ 1.06 (t, J = 7.1 Hz, 6 H), 1.79−1.89 (m, 4 H), 2.62−2.73 (m, 11 H), 3.72 (s, 3 H), 4.30 (s, 2 H), 4.57−4.65 (m, 2 H), 6.39 (d, J = 8.8 Hz, 1 H), 6.62 (dd, J = 8.8, 2.0 Hz, 1 H), 6.98 (s, 1 H), 6.99−7.07 (m, 5 H), 7.12−7.17 (m, 2 H), 7.20−7.31 (m, 9 H), 7.34 (d, J = 1.8 Hz, 1 H), 7.79 (d, J = 8.3 Hz, 2 H). ^{1}H NMR for **119**: (400 MHz, acetone-d_6) δ 1.78−1.89 (m, 2 H), 2.61−2.75 (m, 8 H), 3.72 (s, 3 H), 4.31 (s, 2 H), 4.62 (s, 2 H), 6.28 (t, J = 6.1 Hz, 1 H), 6.39 (d, J = 8.8 Hz, 1 H), 6.62 (dd, J = 8.8, 2.3 Hz, 1 H), 6.98 (s, 1 H), 6.99−7.07 (m, 5 H), 7.11−7.18 (m, 2 H), 7.20−7.30 (m, 9 H), 7.34 (d, J = 2.0 Hz, 1 H), 7.79 (d, J = 8.3 Hz, 2 H).

Methyl 4-{3-[2-{2-[({2-[(4-Acetylpiperazin-1-yl)methyl]benzyl}sulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoate (121). Compound **12** was reacted with 1-acetylpiperazine to afford sulfonamide **121** in 75% as a white foam. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.80−1.88 (m, 4 H), 2.09−2.15 (m, 2 H), 2.16−2.24 (m, 2 H), 2.62−2.75 (m, 8 H), 3.22−3.27 (m, 2 H), 3.27−3.32 (m, 2 H), 3.50 (s, 2 H), 3.72 (s, 3 H), 4.51 (s, 2 H), 6.33 (t, J = 5.4 Hz, 1 H), 6.38 (d, J = 8.8 Hz, 1 H), 6.62 (dd, J = 8.8, 2.3 Hz, 1 H), 6.97 (s, 1 H), 6.99−7.03 (m, J = 7.6, 1.8 Hz, 4 H), 7.04−7.09 (m, J = 5.3 Hz, 1 H), 7.11−7.15 (m, 2 H), 7.18 (d, J = 7.6 Hz, 1 H), 7.22−7.26 (m, 8 H), 7.35 (d, J = 1.8 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 2 H).

Methyl 4-[3-(5-Chloro-1-(diphenylmethyl)-2-{2-[({2-[(4-methylpiperazin-1-yl)methyl]benzyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)propyl]benzoate (123). Compound **12** was reacted with 1-methylpiperazine to afford **123** in 84% as a white solid.

Procedure B: Ester Hydrolysis. 4-(2-{1-Benzhydryl-5-chloro-2-[2-({[(phenylsulfanyl)methyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (26). Ester **14** (30 mg, 0.041 mmol) was hydrolyzed in 15%NaOH/THF/MeOH (2.4 mL, 1:1:1, v/v) overnight. The reaction mixture was acidified to ∼pH 3 with HCl, extracted with EtOAc, dried ($MgSO_4$), and evaporated to give the title acid (27 mg, 93%) as a solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 3.22−3.33 (m, 6 H), 4.31 (t, J = 6.7 Hz, 2 H), 4.40 (s, 2 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.71 (t, J = 5.4 Hz, 1 H), 6.78 (dd, J = 8.8, 2.2 Hz, 1 H), 7.01 (d, J = 9.1 Hz, 2 H), 7.12−7.18 (m, 5 H), 7.21−7.29 (m, 3 H), 7.33−7.39 (m, 6 H), 7.46−7.54 (m, 2 H), 7.68 (d, J = 1.6 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H), 709.11. HRMS calcd for [$C_{39}H_{35}ClN_2O_5S_2$ − H] 709.160 31; found 709.159 99.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2-chlorophenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (27). Ester **15** was hydrolyzed to afford **27** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (d, J = 6.8 Hz, 2 H), 3.07−3.35 (m, 4 H), 4.09 (s, 2 H), 4.24 (t, J = 6.3 Hz, 2 H), 4.78 (t, 1 H), 6.53 (d, J = 9.1 Hz, 1 H), 6.73−6.98 (m, 4 H), 7.02−7.21 (m, 6 H), 7.22−7.41 (m, 7 H), 7.49 (dd, J = 7.1, 1.9 Hz, 1 H), 7.55 (d, J = 1.9 Hz, 1 H), 7.99 (d, J = 8.7 Hz, 2 H). HRMS calcd for [$C_{39}H_{34}Cl_2N_2O_5S_2$ − H] 743.121 34; found 743.121 11.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2-methylphenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (28). Ester **16** was hydrolyzed to afford **28** in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.89−3.01 (m, 2 H), 3.07−3.16 (m, 2 H), 3.21 (t, J = 6.3 Hz, 2 H), 4.02 (s, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.63 (t, J = 5.5 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.79−6.94 (m, 4 H), 7.01−7.17 (m, 7 H), 7.27−7.35 (m, J = 2.7 Hz, 6 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.54 (s, 1 H), 8.00 (d, J = 9.1 Hz, 2 H). HRMS calcd for [$C_{40}H_{37}ClN_2O_5S$ − H] 723.175 96; found 723.175 96.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,6-dimethylphenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (29). Ester **17** was hydrolyzed to afford **29** in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 6 H), 2.84−2.96 (m, 2 H), 3.05−3.15 (m, 2 H), 3.22 (t, J = 6.5 Hz, 2 H), 3.80 (s, 2 H), 4.23 (t, J = 6.6 Hz, 2 H), 4.46 (t, J = 5.4 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.79−6.92 (m, 4 H), 7.02−7.14 (m, 7 H), 7.24−7.36 (m, 7 H), 7.55 (d, J = 1.9 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}ClF_2N_2O_5S_2$ + H^+], 739.2067; found 739.2056.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,5-dimethoxyphenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (30). Ester **18** was hydrolyzed to afford **30** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ2.90−3.01 (m, 2 H), 3.02−3.12 (m, 2 H), 3.20 (t, J = 6.2 Hz, 2 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 4.13 (s, 2 H), 4.22 (t, J = 6.3 Hz, 2 H), 4.91−4.99 (m, 1 H), 6.50 (d, J = 9.1 Hz, 1 H), 6.68−6.93 (m, 6 H), 7.00−7.12 (m, 5 H), 7.27−7.35 (m, J = 3.3 Hz, 7 H), 7.55 (s, 1 H), 7.99 (d, J = 8.5 Hz, 2 H). HRMS calcd for [$C_{41}H_{39}ClN_2O_7S_2$ − H] 769.181 44; found 769.181 21.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,4-difluorophenyl)thio]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (31). Ester **19** was hydrolyzed to afford **31** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99−3.09 (m, 2 H), 3.12−3.20 (m, 2 H), 3.24 (t, J = 6.0 Hz, 2 H), 3.92 (d, J = 1.1 Hz, 2 H), 4.25 (t, J = 6.3 Hz, 2 H), 4.73 (t, J = 5.9 Hz, 1 H), 6.50−6.58 (m, 1 H), 6.72−6.97 (m, 6 H), 7.03−7.13 (m, J = 4.1 Hz, 4 H), 7.28−7.36 (m, 6 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.96−8.04 (m, 2 H). HRMS calcd for [$C_{39}H_{33}ClF_2N_2O_5S_2$ + H^+], 747.1566; found 747.1556.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,4-dichlorophenyl)sulfanyl]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (32). Ester **20** was hydrolyzed to afford **32** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ2.98−3.11 (m, 2 H), 3.12−3.20 (m, 2 H), 3.24 (t, J = 6.3 Hz, 2 H), 4.03 (s, 2 H), 4.25 (t, J = 6.5 Hz, 2 H), 4.84 (t, J = 5.8 Hz, 1 H), 6.54 (d, J = 9.1 Hz, 1 H), 6.80−6.96 (m, 6 H), 7.04−7.15 (m, 5 H), 7.27−7.34 (m, 5 H), 7.43 (d, J = 8.5 Hz, 1

H), 7.55 (d, J = 1.9 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S_2$ + H^+], 779.0974; found 779.0961.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(2,6-dichlorophenyl)sulfanyl]-methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (33). Ester **21** was hydrolyzed to afford **33** in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91−3.02 (m, 2 H), 3.10−3.20 (m, 2 H), 3.25 (t, J = 6.2 Hz, 2 H), 4.03 (s, 2 H), 4.25 (t, J = 6.3 Hz, 2 H), 4.96 (t, J = 6.6 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.81−6.94 (m, 4 H), 7.05−7.13 (m, 4 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.32 (dd, J = 6.5, 2.1 Hz, 8 H), 7.58 (s, 1 H), 8.01 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S_2$ − H] 777.082 37; found 777.082 05.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3,5-dichlorophenyl)sulfanyl]-methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (34). Ester **22** was hydrolyzed to afford **34** in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00−3.30 (m, 6 H), 4.02 (s, 2 H), 4.21−4.30 (m, 2 H), 4.70−4.79 (m, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.80−6.90 (m, 3 H), 6.94 (s, 1 H), 7.03−7.13 (m, J = 3.8 Hz, 4 H), 7.20−7.24 (m, 1 H), 7.27−7.35 (m, 8 H), 7.55 (s, 1 H), 7.95−8.04 (m, 2 H). HRMS calcd for [$C_{39}H_{33}Cl_3N_2O_5S_2$ − H] 777.082 37; found 777.081 59.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3-chloro-4-fluorophenyl)thio]-methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (35). Ester **23** was hydrolyzed to afford **35** in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ2.95−3.30 (m, 6 H), 3.98 (s, 2 H), 4.25 (t, J = 5.6 Hz, 2 H), 4.80−4.91 (m, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.78−6.95 (m, 4 H), 7.03−7.11 (m, 4 H), 7.27−7.34 (m, 9 H), 7.55 (s, 1 H), 7.94−8.03 (m, 2 H). HRMS calcd for $C_{39}H_{33}Cl_2FN_2O_5S_2$, 762.1192; found [M + H]$^{1+}$ 763.1258.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3,4-dichlorophenyl)thio]methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (36). Ester **24** was hydrolyzed to afford **36** in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01−3.11 (m, J = 9.6 Hz, 2 H), 3.12−3.20 (m, J = 7.4 Hz, 2 H), 3.23 (t, J = 5.6 Hz, 2 H), 4.00 (s, 2 H), 4.25 (t, J = 6.0 Hz, 2 H), 4.78 (s, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.79−6.90 (m, 3 H), 6.94 (s, 1 H), 7.08 (d, J = 4.1 Hz, 4 H), 7.28−7.36 (m, 8 H), 7.50−7.57 (m, 2 H), 7.99 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{39}H_{33}Cl_3N_2O_5S_2$, 778.0896; found [M + H]$^{1+}$ 779.0966.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({[(3,4-dichlorophenyl)sulfinyl]-methyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (38). Ester **25** was hydrolyzed to afford **38** in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08−3.29 (m, J = 14.4 Hz, 6 H), 4.13 (s, 2 H), 4.19−4.27 (m, J = 6.3 Hz, 2 H), 5.77 (s, 1 H), 6.48−6.53 (m, 1 H), 6.78−6.86 (m, 3 H), 6.96 (s, 1 H), 7.06−7.15 (m, 4 H), 7.25−7.39 (m, 7 H), 7.54−7.62 (m, 2 H), 7.66−7.71 (m, 1 H), 7.88−7.94 (m, 2 H). HRMS calcd for $C_{39}H_{33}Cl_3N_2O_6S_2$ + Na^+, 817.0744; found 817.0732.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[(methylsulfonyl)methyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (40). Ester **133** was hydrolyzed to afford **40** in 95% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 2.99−3.43 (m, 9 H), 4.29 (t, J = 6.2 Hz, 2 H), 4.67−4.83 (m, 2 H), 6.46 (d, J = 9.1 Hz, 1 H), 6.72 (dd, J = 9.1, 1.9 Hz, 1 H), 6.93 (d, J = 9.1 Hz, 2 H), 7.11 (dd, J = 6.6, 2.5 Hz, 5 H), 7.23−7.41 (m, 6 H), 7.59 (d, J = 1.6 Hz, 1 H), 7.91 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{34}H_{33}ClN_2O_7S_2$, 680.1418; found [M + H]$^{1+}$ 681.1477.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-morpholinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (99). Ester **63** (36 mg, 0.050 mmol) was hydrolyzed to give **99** in 89% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.87 (br s, 4 H), 3.13 (m, 2 H), 3.32 (m, 6 H), 3.47 (br s, 2 H), 3.78 (br s, 4 H), 4.33 (t, J = 6.5 Hz, 2 H), 6.55 (d, J = 8.7 Hz, 1 H), 6.78 (dd, J = 8.9, 2.0 Hz, 1 H), 7.01 (d, J = 7.1 Hz, 2 H), 7.18−7.20 (m, 4 H), 7.24 (s, 1 H), 7.34−7.36 (m, 6 H), 7.70 (d, J = 2.2 Hz, 1 H), 7.94 (d, J = 8.7 Hz, 2 H). HRMS calcd for [$C_{38}H_{40}ClN_3O_6S$ − H] 700.2535; found 700.225 00.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (76). Ester **41** was hydrolyzed to afford **76** in 61% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.85 (br s, 2 H), 3.15−3.25 (m, 2 H), 3.31 (t, J = 6.3 Hz, 2 H), 3.49 (t, J = 7.5 Hz, 2 H), 4.33 (t, J = 6.5 Hz, 2 H), 4.50 (t, J = 6.8 Hz, 2 H), 6.17 (m, 1 H), 6.42 (m, 1 H), 6.56 (d, J = 8.7 Hz, 1 H), 6.79 (dd, J = 8.7, 2.20 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 2 H), 7.13−7.20 (m, 4 H), 7.36−7.45 (m, 6 H), 7.63 (d, J = 1.7 Hz, 1 H), 7.69 (d, J = 1.7 Hz, 1 H), 7.95 (d, J = 9.0 Hz, 2 H). HRMS calcd for [$C_{37}H_{35}ClN_4O_5S$ − H] 681.194 39; found 681.194 07.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3-methyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (77). Ester **42** was hydrolyzed to afford **77** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3 H), 2.18 (d, J = 2.2 Hz, 1 H), 2.25 (d, J = 2.4 Hz, 1 H), 2.44 (d, J = 2.2 Hz, 1 H), 2.91 (m, 2 H), 3.07 (m, 2 H), 3.21 (t, J = 6.4 Hz, 2 H), 3.37 (t, J = 6.4 Hz, 2 H), 4.19 (t, J = 6.4 Hz, 2 H), 4.43 (m, 2 H), 4.74 (m, 1 H), 6.49 (d, J = 8.7 Hz, 1 H), 6.80 (m, 2 H), 6.90 (s, 1 H), 7.08 (s, 3 H), 7.27 (m, 7 H), 7.58 (m, 2 H), 7.95 (m, 2 H). HRMS calcd for [$C_{38}H_{37}ClN_4O_5S$ − H] 695.210 04; found 695.209 51.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-methyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (78). Ester **43** was hydrolyzed to afford **78** in 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3 H), 2.85−2.97 (m, 2 H), 3.02−3.13 (m, J = 8.0, 8.0 Hz, 2 H), 3.36 (t, J = 6.2 Hz, 2 H), 4.20 (t, J = 6.5 Hz, 2 H), 4.44 (t, J = 6.2 Hz, 2 H), 4.79 (s, 1 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.76−6.85 (m, J = 8.5 Hz, 3 H), 6.89 (s, 1 H), 7.02−7.18 (m, 6 H), 7.30 (dd, J = 3.0, 1.6 Hz, 6 H), 7.57 (d, J = 1.1 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{38}H_{37}ClN_4O_5S$ − H] 695.210 04; found 695.209 54.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (79). Ester **44** was hydrolyzed to afford **79** in 62% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.93 (s, 5 H), 2.08 (s, 3 H), 3.06−3.14 (m, 4 H), 3.19 (t, J = 6.9 Hz, 2 H), 3.30 (t, J = 6.7 Hz, 2 H), 4.20 (q, J = 7.1 Hz, 4 H), 6.31 (s, 1 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.66 (d, J = 10.4 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.99−7.11 (m, 5 H), 7.17−7.29 (m, 5 H), 7.56 (s, 1 H), 7.82 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{39}H_{39}ClN_4O_5S$ − H] 709.225 69; found 709.225 32.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-imidazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (80). Ester **45** was hydrolyzed to afford **80** in 60% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 4 H), 3.89−3.99 (m, 2 H), 4.00−4.23 (m, 6 H), 4.90−5.05 (m, J = 6.9 Hz, 4 H), 7.21 (d, J = 8.8 Hz, 1 H), 7.51−7.60 (m, 2 H), 7.61−7.69 (m, J = 8.5 Hz, 2 H), 7.80−7.88 (m, J = 7.7 Hz, 5 H), 7.91 (s, 1 H), 8.04−8.15 (m, 5 H), 8.34−8.45 (m, 3 H), 8.56 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{37}H_{35}ClN_4O_5S$ − H] 681.194 39; found 681.194 09.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-1,2,4-triazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (81). Ester **46** was hydrolyzed to afford **81** in 100% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.99−3.11 (m, 4 H), 3.14−3.26 (m, 2 H), 3.44−3.55 (m, 2 H), 4.17−4.30 (m, 2 H), 4.44−4.55 (m, 2 H), 5.76 (s, 1 H), 6.47 (d, J = 8.0 Hz, 1 H), 6.81 (d, J = 6.0 Hz, 1 H), 6.98 (d, J = 8.2 Hz, 1 H), 7.03−7.15 (m, 5 H), 7.26−7.43 (m, 6 H), 7.53−7.71 (m, J = 23.9 Hz, 2 H), 7.85 (d, J = 8.8 Hz, 2 H), 7.93 (s, 1 H), 8.50 (s, 1 H). HRMS calcd for [$C_{36}H_{34}ClN_5O_5S$ − H] 682.189 64; found 682.189 64.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-1,2,3-triazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (82). Ester **47** was hydrolyzed to afford **82** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85−3.00 (m, 2 H), 3.07−3.25 (m, J = 25.0 Hz, 4 H), 3.31−3.40 (m, 2 H), 4.17−4.26 (m, 2 H), 4.61−4.71 (m, 2 H), 5.06 (s, 1 H), 6.45−6.55 (m, 1 H), 6.76−6.94 (m, 4 H), 7.07 (d, J = 2.5 Hz, 4 H), 7.25−7.33 (m, J = 4.4, 1.9 Hz, 6 H), 7.50−7.56 (m, 2 H), 7.58−7.64 (m, 1 H), 7.90−7.99 (m, 2 H). HRMS calcd for [$C_{36}H_{34}ClN_5O_5S$ − H] 682.189 64; found 682.189 33.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2*H*-tetraazol-2-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (83). Ester **48** was hydrolyzed to afford **83** in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84−2.96 (m, 2 H), 3.09−3.18 (m, 2 H), 3.23 (t, J = 5.5 Hz, 2 H), 3.39−3.49 (m, 2 H), 4.26 (t, J = 5.5 Hz, 2 H), 4.57−4.65 (m, 1 H), 4.88−4.97 (m, 2 H), 6.52−6.58 (m, 1 H), 6.80−6.93 (m, 4 H), 7.07 (dd, J = 6.2, 2.9 Hz, 4 H), 7.27−7.37 (m, 6 H), 7.55 (d, J = 1.9 Hz, 1 H), 7.95−7.96 (m, 2 H), 8.37−8.41 (m, 1 H). HRMS calcd for [$C_{35}H_{33}ClN_6O_5S$ − H] 683.184 89; found 683.184 35.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1*H*-tetraazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (84). Ester **49** was hydrolyzed to afford **84** in 83% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.02−3.13 (m, 4 H), 3.15−3.25 (m, 2 H), 3.54−3.69 (m, 2 H), 4.18−4.31 (m, 2 H), 4.78 (t, J = 6.5 Hz, 2 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.9, 2.1 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.04−7.15 (m, 5 H), 7.29−7.42 (m, 6 H), 7.67 (d, J = 1.9 Hz, 2 H), 7.85 (d, J = 8.8 Hz, 2 H). HRMS calcd for [$C_{35}H_{33}ClN_6O_5S$ − H] 683.184 89; found 683.184 35.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1-piperidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (86). Ester **50** was hydrolyzed to afford **86** in 92% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.39 (s, 2 H), 1.53 (s, 4 H), 2.48 (s, 4 H), 2.72−2.86 (m, 2 H), 3.26−3.38 (m, 8 H), 4.29 (s, 2 H), 6.55 (d, J = 8.7 Hz, 1 H), 6.77 (d, J = 9.0 Hz, 1 H), 6.97 (m, 2 H), 7.19 (m, 5 H), 7.33 (m, 6 H), 7.69 (s, 1 H), 7.91 (d, J = 7.4 Hz, 2 H). HRMS calcd for [$C_{39}H_{42}ClN_3O_5S$ − H] 698.246 09; found 698.245 70.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-methyl-1-piperidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (87). Ester **51** was hydrolyzed to afford **87** in 96% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.30−1.50 (m, 5 H), 1.65−85 (m, 4 H), 2.8−3.2 (m, 2 H), 3.0−3.2 (m, 2 H), 3.25−3.45 (m, 6 H), 3.5−3.8 (m, 3 H), 4.34 (t, J = 6.5 Hz, 2 H), 6.53 (d, J = 8.7 Hz, 1 H), 6.77 (dd, J = 8.9, 2.0 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 2 H), 7.18−7.23 (m, 4 H), 7.29 (s, 1 H), 7.3−7.4 (m, 6 H), 7.69 (d, J = 2.2 Hz, 1 H), 7.94 (d, J = 8.7 Hz, 2 H). HRMS calcd for [$C_{40}H_{44}ClN_3O_5S$ − H] 712.261 74; found 712.261 13.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3-methylpiperidin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (88). Ester **52** was hydrolyzed to afford **88** in 87% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.69−0.84 (m, 3 H), 1.25−1.83 (m, 4 H), 2.40−2.65 (m, 4 H), 2.97−3.17 (m, 6 H), 3.21 (t, J = 5.8 Hz, 2 H), 3.27−3.44 (m, 6 H), 4.25 (t, J = 6.3 Hz, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 1.9 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.10 (d, J = 7.7 Hz, 4 H), 7.31−7.43 (m, 6 H), 7.68 (d, J = 1.9 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{40}H_{44}ClN_3O_5S$, 713.2690; found $[M + H]^{1+}$ 714.2765.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-methylpiperidin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (89). Ester **53** was hydrolyzed to afford **89** in 62% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (d, J = 4.1 Hz, 3 H), 0.91−1.13 (m, 2 H), 1.37−1.87 (m, J = 87.6 Hz, 4 H), 2.54−2.71 (m, 2 H), 2.98−3.15 (m, 6 H), 3.21 (t, J = 6.5 Hz, 2 H), 3.27−3.45 (m, 4 H), 4.24 (t, J = 6.3 Hz, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.2 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.05−7.18 (m, 5 H), 7.31−7.43 (m, 6 H), 7.68 (d, J = 1.9 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{40}H_{44}ClN_3O_5S$, 713.2690; found 714.2755.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[(2*R*,6*S*)-2,6-dimethyl-1-piperidinyl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (90). Ester **54** was hydrolyzed to afford **90** in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74−1.78 (m, 12 H), 2.43−2.68 (m, 2 H), 2.95−3.44 (m, 10 H), 4.05−4.17 (m, 2 H), 6.42−6.65 (m, 4 H), 6.73−6.84 (m, 1 H), 6.96−7.17 (m, 6 H), 7.20−7.35 (m, 4 H), 7.55−7.63 (m, 1 H), 7.71−7.82 (m, J = 7.8, 7.8 Hz, 2 H). HRMS calcd for [$C_{41}H_{46}ClN_3O_5S$ − H] 726.277 39; found 726.277 20.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-thiomorpholinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (91). Ester **55** was hydrolyzed to afford **91** in 90% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.55 (app s, 4 H), 2.59 (app s, 4 H), 2.70 (t, J = 6.8 Hz, 2 H), 3.08 (t, J = 6.87 Hz, 2 H), 3.32 (m, 6 H), 4.33 (m, 2 H), 6.57 (d, J = 9.0 Hz, 1 H), 6.78 (dd, J = 9.1, 2.2 Hz, 2 H), 6.98−7.03 (m, 2 H), 7.13−7.22 (m, 5 H), 7.33−7.40 (m, 6 H), 7.69 (s, 1 H), 7.96 (m, 2 H). HRMS calcd for [$C_{38}H_{40}ClN_3O_5S_2$ − H] 716.202 51; found 716.202 17.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-hydroxy-1-piperidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (92). Ester **56** was hydrolyzed to afford **92** in 42% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.74−2.80 (m, 4 H), 3.69−4.39 (m, 16 H), 4.92−5.04 (m, 2 H), 7.21 (d, J = 9.1 Hz, 1 H), 7.56 (d, J = 9.1 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 2 H), 7.85 (d, J = 7.1 Hz, 5 H), 8.10 (s, 6 H), 8.42 (s, 1 H), 8.60 (d, J = 8.5 Hz, 2 H). HRMS calcd for [$C_{39}H_{42}ClN_3O_6S$ − H] 714.241 00; found 714.240 85.

4-{2-[1-Benzhydryl-5-chloro-2-(2-{[(2-{2-[(dimethylamino)methyl]-1-piperidinyl}ethyl)sulfonyl]amino}ethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (93). Ester **57** was hydrolyzed to afford **93** in 79% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (m, 4 H), 3.30 (m, 4 H), 3.46 (m, 2 H), 3.70 (m, 2 H), 3.88 (m, 4 H), 3.96 (m, 2 H), 4.15 (m, 2 H), 5.04 (m, 1 H), 7.27 (d, J = 9.0 Hz, 1 H), 7.61 (dd, J = 8.9, 2.0 Hz, 1 H), 7.79 (m, 2 H), 7.91 (m, 5 H), 8.15 (m, 6 H), 8.48 (d, J = 1.9 Hz, 1 H), 8.65 (d, J = 8.7 Hz, 2 H). HRMS calcd for [$C_{42}H_{49}ClN_4O_5S$ − H] 755.303 94; found 755.303 44.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[4-(2-pyridinyl)-1-piperazinyl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (94). Ester **58** was hydrolyzed to afford **94** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43−2.55 (m, 4 H), 2.76−2.87 (m, 2 H), 2.96−3.11 (m, 4 H), 3.13−3.29 (m, J = 6.6 Hz, 4 H), 3.31−3.43 (m, 4 H), 4.15−4.26 (m, 2 H), 6.45−6.58 (m, 2 H), 6.66 (d, J = 6.6 Hz, 1 H), 6.74−6.85 (m, 3 H), 6.93−6.99 (m, 1 H), 7.08 (d, J = 7.4 Hz, 5 H), 7.21−7.34 (m, 5 H), 7.42−7.56 (m, 2 H), 7.88−7.97 (m, 2 H), 8.14−8.22 (m, J = 4.9 Hz, 1 H). HRMS calcd for [$C_{43}H_{44}ClN_5O_5S$ − H] 776.267 89; found 776.267 50.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3,5-dimethylpiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (95). Ester **59** was hydrolyzed to afford **95** in 39% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (d, J = 6.3 Hz, 6 H), 1.61 (t, J = 10.9 Hz, 2 H), 2.52−2.56 (m, 2 H), 2.61−2.67 (m, 2 H), 2.79−2.89 (m, 2 H), 3.00−3.10 (m, 6 H), 3.16−3.23 (m, 2 H), 4.24 (t, J = 6.2 Hz, 2 H), 6.47 (d, J = 9.1 Hz, 1 H), 6.81 (dd, J = 8.8, 1.9 Hz, 1 H), 6.96 (d, J = 9.1 Hz, 2 H), 7.07−7.13 (m, J = 7.4, 1.9 Hz, 5 H), 7.31−7.39 (m, 6 H), 7.67 (d, J = 1.9 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{40}H_{45}ClN_4O_5S$, 728.2799; found $[M + H]^{1+}$ 729.2873.

4-(2-{2-[2-({[2-(4-Acetyl-3,5-dimethylpiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1-benzhydryl-5-chloro-1*H*-indol-3-yl}ethoxy)benzoic Acid (96). Ester **60** was hydrolyzed to afford **96** in 96% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.18 (d, 6 H), 1.95−1.97 (m, 3 H), 1.98 (d, J = 3.3 Hz, 2 H), 2.62−2.74 (m, 2 H), 2.82−2.93 (m, 4 H), 3.08−3.23 (m, 2 H), 3.27−3.38 (m, J = 6.6, 6.6 Hz, 6 H), 4.35 (t, J = 6.7 Hz, 2 H), 6.56 (d, J = 9.1 Hz, 1 H), 6.79 (dd, J = 8.9, 2.1 Hz, 1 H), 7.03 (d, J = 8.8 Hz, 2 H), 7.16−7.24 (m, 5 H), 7.37 (dd, J = 5.1, 1.8 Hz, 6 H), 7.70 (d, J = 1.9 Hz, 1 H), 7.95 (d, J = 9.1 Hz, 2 H). HRMS calcd for $C_{42}H_{47}ClN_4O_6S$, 770.2905; found $[M + H]^{1+}$ 771.2975.

4-(2-{2-[2-({[2-(4-Acetylpiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1-benzhydryl-5-chloro-1*H*-indol-3-yl}ethoxy)benzoic Acid (97). Ester **61** was hydrolyzed to afford **97** in 19% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.93−2.00 (m, J = 2.2 Hz, 3 H), 2.22−2.31 (m, J = 4.9, 4.9 Hz, 2 H), 2.31−2.39 (m, 2 H), 2.64−2.74 (m, 2 H), 3.11 (t, J = 6.9 Hz, 2 H), 3.27−3.42 (m, 10 H), 4.35 (t, J = 6.7 Hz, 2 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.79 (dd, J = 9.1, 1.9 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.14−7.23 (m, J = 7.8, 4.8 Hz, 5 H), 7.32−7.42 (m, 6 H), 7.69 (d, J = 2.2 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{40}H_{43}ClN_4O_4S$, 742.2592; found 743.2664.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-methyl-3-oxopiperazin-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (98). Ester **62** was hydrolyzed to afford **98** in 29% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24−1.31 (m, 3 H), 2.71−2.81 (m, 1 H), 2.89−3.27 (m, 14 H), 4.24 (t, J = 6.4 Hz, 2 H), 5.14 (none, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 6.78−6.85 (m, 3 H), 6.97 (s, 1 H), 7.07−7.13 (m, 4 H), 7.28−7.34 (m, 6 H), 7.55 (d, J = 2.0 Hz, 1 H), 7.90−7.97 (m, 2 H). HRMS calcd for $C_{39}H_{41}ClN_4O_6S$, 728.2435; found $[M + H]^{1+}$ 729.2501.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-oxa-5-azabicyclo[2.2.1]-hept-5-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (100). Ester **64** was hydrolyzed to afford **100** in 100% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 1.60−1.75 (m, 2 H), 2.54 (d, J = 10.6 Hz, 1 H), 2.70 (dd, J = 10.5, 1.4 Hz, 1 H), 2.77−3.08 (m, 9 H), 3.17 (t, J = 6.4 Hz, 2 H), 3.44−3.49 (m, 2 H), 3.77 (t, J = 8.0 Hz, 1 H), 4.20 (t, J = 6.3 Hz, 2 H), 4.27 (s, 1 H), 6.38 (d, J = 8.8 Hz, 1 H), 6.63 (dd, J = 8.8, 2.0 Hz, 1 H), 6.78−6.84 (m, 2 H),

6.97−7.04 (m, 5 H), 7.18−7.25 (m, 6 H), 7.50 (d, J = 2.0 Hz, 1 H), 7.78−7.83 (m, 2 H). HRMS calcd for $C_{39}H_{40}ClN_3O_6S$, 713.2326; found $[M + H]^{1+}$ 714.2397.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[(3*R*,5*S*)-3,5-dimethylmorpholin-4-yl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (101). Ester **65** was hydrolyzed to afford **101** in 8% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 0.98 (d, J = 6.1 Hz, 6 H), 1.51 (t, J = 10.7 Hz, 2 H), 2.45−2.53 (m, 4 H), 2.91−2.97 (m, J = 8.5, 6.4 Hz, 2 H), 3.05−3.11 (m, 2 H), 3.18−3.26 (m, 5 H), 3.38−3.45 (m, J = 3.0 Hz, 1 H), 4.24 (t, J = 5.8 Hz, 2 H), 6.41 (d, J = 9.1 Hz, 1 H), 6.66 (dd, J = 8.8, 2.0 Hz, 1 H), 6.85 (d, J = 9.1 Hz, 2 H), 7.04 (dd, J = 6.9, 2.7 Hz, 5 H), 7.21−7.28 (m, 6 H), 7.54 (d, J = 1.8 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H), 8.32 (s, 1 H). HRMS calcd for $[C_{40}H_{44}ClN_3O_6S + H]$ 730.2717; found 730.2708.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1-pyrrolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (102). Ester **66** was hydrolyzed to afford **102** in 94% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37−2.63 (m, J = 2.7 Hz, 4 H), 3.44−4.26 (m, 14 H), 4.85−5.00 (m, 2 H), 7.14 (dd, J = 8.8, 2.5 Hz, 1 H), 7.44−7.51 (m, 1 H), 7.66 (dd, J = 8.9, 2.6 Hz, 2 H), 7.72−7.85 (m, 5 H), 7.97−8.12 (m, J = 4.4 Hz, 6 H), 8.31−8.38 (m, 1 H), 8.43−8.60 (m, J = 8.8, 2.5 Hz, 2 H). HRMS calcd for $[C_{38}H_{40}ClN_3O_5S - H]$ 684.230 44; found 684.230 09.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-methyl-1-pyrrolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (103). Ester **67** was hydrolyzed to afford **103** in 99% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.48 (br s, 3 H), 1.76 (m, 1 H), 1.96 (m, 2 H), 2.21 (m, 1 H), 3.01 (m, 2 H), 3.25−3.45 (m, 6 H), 3.5−3.7 (m, 4 H), 3.91 (br s, 1 H), 4.34 (t, J = 6.4 Hz, 2 H), 6.53 (d, J = 8.7 Hz, 1 H), 6.77 (dd, J = 8.9, 2.0 Hz, 1 H), 7.02 (d, J = 8.5 Hz, 2 H), 7.21 (m, 4 H), 7.29 (s, 1 H), 7.36 (m, 6 H), 7.69 (d, J = 1.9 Hz, 1 H), 7.94 (d, J = 8.7 Hz, 2 H). HRMS calcd for $[C_{39}H_{42}ClN_3O_5S - H]$ 698.246 09; found 698.245 72.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2,5-dimethyl-1-pyrrolidinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (104). Ester **68** was hydrolyzed to afford **104** in 96% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.9−1.2 (m, 6 H), 1.2−1.5 (m, 2 H), 1.7−1.9 (m, 2 H), 2.7−3.2 (m, 6 H), 4.35 (t, J = 6.6 Hz, 2 H), 6.56 (d, J = 8.7 Hz, 1 H), 6.75−6.81 (m, 1 H), 6.98−7.03 (m, 2 H), 7.16−7.23 (m, 5 H), 7.33−7.38 (m, 6 H), 7.69 (s, 1 H), 7.92−7.97 (m, 2 H). HRMS calcd for $[C_{40}H_{44}ClN_3O_5S - H]$ 712.261 74; found 712.261 14.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(1,3-thiazolidin-3-yl)ethyl]-sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (105). Ester **69** was hydrolyzed to afford **105** in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70−3.31 (m, 14 H), 3.78 (s, 2 H), 4.25 (t, J = 6.7 Hz, 2 H), 6.54 (d, J = 9.1 Hz, 1 H), 6.78−6.92 (m, 3 H), 6.97 (s, 1 H), 7.05−7.16 (m, 5 H), 7.28−7.37 (m, 5 H), 7.56 (s, 1 H), 7.99 (d, J = 8.8 Hz, 2 H). HRMS calcd for $[C_{37}H_{38}ClN_3O_5S_2 - H]$ 702.186 86; found 702.186 59.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(3-hydroxy-1-pyrrolidinyl)-ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (106). Ester **70** was hydrolyzed to afford **106** in 84% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30−3.51 (m, 2 H), 3.67−4.40 (m, 14 H), 4.82−4.91 (m, 1 H), 4.93−5.05 (m, 2 H), 5.52 (s, 1 H), 7.21 (d, J = 8.5 Hz, 1 H), 7.55 (dd, J = 8.9, 2.1 Hz, 1 H), 7.73 (d, J = 8.8 Hz, 2 H), 7.79−7.91 (m, J = 4.9 Hz, 5 H), 8.02−8.20 (m, 6 H), 8.41 (d, J = 1.9 Hz, 1 H), 8.59 (d, J = 8.8 Hz, 2 H). HRMS calcd for $[C_{38}H_{40}ClN_3O_6S - H]$ 700.225 35; found 700.224 90.

4-{2-[5-Chloro-2-{2-[({2-[3-(dimethylamino)pyrrolidin-1-yl]ethyl}sulfonyl)amino]ethyl}-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}benzoic Acid (107). Ester **71** was hydrolyzed to afford **107** in 73% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.97−3.48 (m, 8 H), 3.73−4.01 (m, J = 26.9 Hz, 12 H), 4.28−4.42 (m, 4 H), 4.93−5.05 (m, 2 H), 7.22 (d, J = 8.8 Hz, 1 H), 7.52−7.59 (m, J = 2.2 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.79−7.90 (m, 5 H), 8.09 (s, 6 H), 8.42 (d, J = 1.9 Hz, 1 H), 8.59 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{40}H_{45}ClN_4O_5S + H^+$, 729.2877; found 729.2872.

4-[2-(1-Benzhydryl-5-chloro-2-{2-[({2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]ethyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)ethoxy]benzoic Acid (108). Ester **72** was hydrolyzed to afford **108** in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49−1.90 (m, 4 H), 2.11−2.21 (m, 1 H), 2.60−2.74 (m, 2 H), 2.88−3.41 (m, 15 H), 3.48 (dd, J = 10.1, 3.3 Hz, 1 H), 4.24 (t, J = 6.8 Hz, 2 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 2.0 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.98−7.02 (m, 1 H), 7.08−7.18 (m, 5 H), 7.29−7.36 (m, 5 H), 7.58 (d, J = 2.0 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 2 H). HRMS calcd for $C_{40}H_{44}ClN_3O_6S$, 729.2639; found $[M + H]^{1+}$ 730.2709.

4-{2-[2-{2-[({2-[(2*S*)-2-(Aminocarbonyl)pyrrolidin-1-yl]ethyl}sulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]ethoxy}-benzoic Acid (109). Ester **73** was hydrolyzed to afford **109** in 43% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50−1.67 (m, 4 H), 1.87−2.14 (m, 2 H), 2.51−3.47 (m, 12 H), 4.24 (t, J = 6.8 Hz, 2 H), 6.48 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.0 Hz, 1 H), 6.96−7.01 (m, 2 H), 7.05−7.14 (m, 5 H), 7.27−7.52 (m, 7 H), 7.67 (d, J = 2.0 Hz, 1 H), 7.82−7.87 (m, 2 H), 8.16 (s, 1 H). HRMS calcd for $C_{39}H_{41}ClN_4O_6S$, 728.2435; found $[M + H]^{1+}$ 729.2510.

4-(2-{1-Benzhydryl-5-chloro-2-[2-({[2-(2-thioxo-1-imidazolidinyl)-ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}ethoxy)benzoic Acid (110). Ester **74** was hydrolyzed to afford **110** in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98−3.30 (m, 8 H), 3.45−3.72 (m, J = 31.3 Hz, 4 H), 3.81−3.94 (m, 2 H), 4.18−4.32 (m, 2 H), 5.92 (s, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.75−7.00 (m, 3 H), 7.02−7.16 (m, 4 H), 7.22−7.37 (m, 6 H), 7.55 (dd, J = 5.2, 2.2 Hz, 1 H), 7.92−8.03 (m, 2 H). HRMS calcd for $[C_{37}H_{37}ClN_4O_5S - H]$ 715.182 11; found 715.181 61.

4-(3-{1-Benzhydryl-5-chloro-2-[2-({[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoic Acid (114). Ester **111** was hydrolyzed to afford **114** in 89% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.95−2.10 (m, 2H), 2.18 (s, 3H), 2.20 (s, 3 H), 2.84 (m, 4 H), 3.12 (app d, J = 2.4 Hz, 4 H), 3.42 (m, 2 H), 4.30 (t, J = 6.8 Hz, 2 H), 5.76 (m, 1 H) 6.37 (m, 1 H), 6.52 (d, J = 8.7 Hz, 1 H), 6.76 (dd, J = 8.7, 2.2 Hz, 1 H), 7.15 (m, 4 H), 7.36 (m, 6 H), 7.50 (m, 1 H), 7.63 (dd, J = 5.7, 3.3 Hz, 1 H), 7.79 (dd, J = 5.7, 3.3 Hz, 1 H), 7.96 (m, 2 H). HRMS calcd for $[C_{40}H_{41}ClN_4O_4S - H]$ 707.246 42; found 707.245 97.

4-(3-{1-Benzhydryl-5-chloro-2-[2-({[2-(4-morpholinyl)ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoic Acid (115). Ester **112** was hydrolyzed to afford **115** in 85% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.95−2.05 (m, 2H), 2.85 (m, 4 H), 3.05−3.25 (m, 6 H), 3.25−3.40 (m, 4 H), 3.62 (br s, 2 H), 3.89 (br s, 4 H), 6.50 (d, J = 8.7 Hz, 1 H), 6.75 (dd, J = 8.7, 2.2 Hz, 1 H), 7.197−7.23 (m, 6 H), 7.32−7.40 (m, 7 H), 7.51 (d, J = 2.2 Hz, 1 H), 7.94 (d, J = 7.9 Hz, 2 H). HRMS calcd for $[C_{39}H_{42}ClN_3O_5S - H]$ 698.246 09; found 698.245 81.

4-(3-{1-Benzhydryl-5-chloro-2-[2-({[2-(2,6-dimethyl-1-piperidinyl)-ethyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoic Acid (116). Ester **113** was hydrolyzed to afford **116** in 86% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.35 (d, J = 6.3 Hz, 6 H), 1.75−1.86 (m, J = 7.7 Hz, 4 H), 1.91−2.02 (m, 2 H), 2.75−2.91 (m, 4 H), 3.09−3.20 (m, J = 7.7 Hz, 4 H), 3.23−3.32 (m, 2 H), 3.37−3.55 (m, 4 H), 3.61−3.71 (m, 2 H), 6.51 (d, J = 9.1 Hz, 1 H), 6.73−6.78 (m, 1 H), 7.12−7.17 (m, 5 H), 7.31−7.36 (m, 8 H), 7.49 (d, J = 2.2 Hz, 1 H), 7.92 (d, J = 8.2 Hz, 2 H). HRMS calcd for $C_{42}H_{48}ClN_3O_4S + H^+$, 726.3132; found 726.3125.

4-{3-[5-Chloro-1-(diphenylmethyl)-2-(2-{[(2-formylbenzyl)sulfonyl]-amino}ethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (125). Ester **12** was hydrolyzed to afford **125** in 62% as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.82−1.89 (m, 2 H), 2.59−2.74 (m, 8 H), 4.76 (s, 2 H), 6.26 (t, J = 5.2 Hz, 1 H), 6.39 (d, J = 8.6 Hz, 1 H), 6.62 (dd, J = 8.8, 2.3 Hz, 1 H), 6.97 (s, 1 H), 6.99−7.04 (m, 4 H), 7.18−7.29 (m, 8 H), 7.31−7.38 (m, 2 H), 7.41−7.45 (m, 2 H), 7.74−7.79 (m, 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 10.10 (s, 1 H). HRMS calcd for $C_{41}H_{37}ClN_2O_5S + H^+$, 705.21845; found $[M + H]^{1+}$ 705.2168.

4-{3-[5-Chloro-2-{2-[({2-[(diethylamino)methyl]benzyl}sulfonyl)-amino]ethyl}-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (126). Ester **118** was hydrolyzed to afford **126** in 66% as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.07 (t, J = 7.0 Hz, 6 H), 1.79−1.89 (m, 4 H), 2.63−2.75 (m, 6 H), 2.93−3.05 (m, 4 H), 3.82−3.98 (m, 2 H), 4.61 (s, 2 H), 6.38 (d, J = 8.8 Hz, 1 H), 6.62 (dd, J = 8.8, 2.2 Hz, 1 H), 7.00−7.06 (m, J = 7.4, 1.6 Hz, 5 H), 7.15−7.21 (m, 3 H), 7.21−7.27 (m, 9 H), 7.35 (d, J = 2.0 Hz, 1

H), 7.83 (d, $J = 8.0$ Hz, 2 H). HRMS calcd for $C_{45}H_{48}ClN_3O_4S + H^+$, 762.312 68; found 762.3133.

4-(3-{5-Chloro-1-(diphenylmethyl)-2-[2-({[2-(hydroxymethyl)benzyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoic Acid (127). Ester **119** was hydrolyzed to afford **127** in 61% as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.80−1.90 (m, 2 H), 2.60−2.76 (m, 6 H), 4.31 (s, 2 H), 4.62 (s, 2 H), 6.28 (t, $J = 6.1$ Hz, 1 H), 6.36−6.41 (m, 1 H), 6.62 (dd, $J = 8.8$, 2.3 Hz, 1 H), 6.98 (s, 1 H), 6.99−7.07 (m, 5 H), 7.12−7.18 (m, 2 H), 7.12−7.18 (m, 2 H), 7.21−7.30 (m, 9 H), 7.35 (d, $J = 2.0$ Hz, 1 H), 7.83 (d, $J = 8.3$ Hz, 2 H). HRMS calcd for $C_{41}H_{39}ClN_2O_5S + H^+$, 707.234 10; found 707.2356.

4-(3-{5-Chloro-1-(diphenylmethyl)-2-[2-({[2-(morpholin-4-ylmethyl)benzyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoic Acid (128). Ester **120** was hydrolyzed to afford **128** in 83% as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.78−1.90 (m, 4 H), 2.18 (brs, 2 H), 2.62−2.76 (m, 6 H), 2.97 (br s, 2 H), 3.44 (d, $J = 6.3$ Hz, 6 H), 4.53 (br s, 2 H), 6.38 (d, $J = 8.8$ Hz, 1 H), 6.62 (dd, $J = 8.8$ Hz, 1 H), 6.97−7.27 (m, 17 H), 7.35 (d, $J = 2.3$ Hz, 1 H), 7.83 (d, $J = 8.3$ Hz, 2 H). HRMS calcd for $C_{45}H_{46}ClN_3O_5S + H^+$, 776.291 95; found $[M + H]^{1+}$ 776.2921.

4-{3-[2-{2-[({2-[(4-Acetylpiperazin-1-yl)methyl]benzyl}sulfonyl)amino]ethyl}-5-chloro-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic Acid (129) and 4-(3-{5-Chloro-1-(diphenylmethyl)-2-[2-({[2-(piperazin-1-ylmethyl)benzyl]sulfonyl}amino)ethyl]-1*H*-indol-3-yl}propyl)benzoic Acid (130). Ester **121** was hydrolyzed to afford, after preparative HPLC separation, **129** (21%) and **130** (21%), both as solids. **129**: ^{1}H NMR (400 MHz, acetone-d_6) δ 1.84 (s, 3 H), 1.85−1.90 (m, 4 H), 2.12−2.19 (m, 2 H), 2.20−2.27 (m, 2 H), 2.64−2.76 (m, 4 H), 3.24−3.29 (m, 2 H), 3.29−3.34 (m, 2 H), 3.53 (s, 2 H), 3.71 (d, $J = 1.5$ Hz, 1 H), 4.52 (s, 2 H), 6.39 (d, $J = 8.8$ Hz, 1 H), 6.63 (dd, $J = 8.8$, 2.0 Hz, 1 H), 6.99 (s, 1 H), 7.00−7.04 (m, $J = 7.6$, 1.8 Hz, 4 H), 7.04−7.11 (m, $J = 8.8$ Hz, 1 H), 7.12−7.17 (m, 2 H), 7.18−7.26 (m, 8 H), 7.35−7.38 (m, 1 H), 7.84 (d, $J = 8.6$ Hz, 2 H), 8.00 (s, 1 H). HRMS calcd for $C_{47}H_{49}ClN_4O_5S + H^+$, 817.318 49; found $[M + H]^{1+}$ 817.3199. **130**: ^{1}H NMR (400 MHz, acetone-d_6) δ 1.85−1.90 (m, 4 H), 1.96 (s, 3 H), 2.12−2.19 (m, 2 H), 2.23 (none, 1 H), 2.20−2.27 (m, 2 H), 2.64−2.76 (m, 4 H), 3.24−3.29 (m, 2 H), 3.29−3.34 (m, 2 H), 3.53 (s, 2 H), 3.71 (d, $J = 1.5$ Hz, 1 H), 4.52 (s, 2 H), 6.39 (d, $J = 8.8$ Hz, 1 H), 6.63 (dd, $J = 8.8$, 2.0 Hz, 1 H), 6.99 (s, 1 H), 7.00−7.04 (m, $J = 7.6$, 1.8 Hz, 4 H), 7.04−7.11 (m, $J = 8.8$ Hz, 1 H), 7.12−7.17 (m, 2 H), 7.18−7.26 (m, 8 H), 7.35−7.38 (m, 1 H), 7.84 (d, $J = 8.6$ Hz, 2 H), 8.00 (s, 1 H). HRMS calcd for $C_{45}H_{47}ClN_4O_4S + H^+$, 775.307 93; found $[M + H]^{1+}$), 775.3073.

4-[3-(5-Chloro-1-(diphenylmethyl)-2-{2-[({2-[(4-methylpiperazin-1-yl)methyl]benzyl}sulfonyl)amino]ethyl}-1*H*-indol-3-yl)propyl]benzoic Acid (131). Ester **123** was hydrolyzed to afford **131** in 69% as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.89−1.97 (m, 2 H), 2.54−2.66 (m, 2 H), 2.70−2.76 (m, 4 H), 2.78 (s, 3 H), 2.80−2.92 (m, 4 H), 3.09−3.16 (m, 4 H), 3.31−3.34 (m, 2 H), 3.66 (s, 2 H), 4.52 (s, 2 H), 6.40 (d, $J = 8.8$ Hz, 1 H), 6.68 (dd, $J = 8.8$, 2.0 Hz, 1 H), 6.96 (s, 1 H), 7.06 (dd, $J = 6.6$, 2.4 Hz, 4 H), 7.14−7.20 (m, 1 H), 7.22−7.26 (m, 2 H), 7.27 (d, $J = 8.3$ Hz, 2 H), 7.31−7.35 (m, 7 H), 7.37 (d, $J = 2.0$ Hz, 1 H), 7.93 (d, $J = 8.3$ Hz, 2 H). HRMS calcd for $C_{46}H_{49}ClN_4O_4S - H^+$, 787.309 03; found $[M - H]^{1-}$ 787.3101.

All assays including GLU micelle, rat whole blood, human whole blood, and MC-9 assays were described previously; the CPE model was also described previously.[4b,c]

All plog$D_{7.4}$ values were calculated from CompuDrug prologD program.

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Supporting Information Available: Purity data from HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Clark, J. D.; Schievella, A. R.; Nalefski, E. A.; Lin, L.-L. Cytosolic phospholipase A_2. *J. Lipid Mediators Cell Signalling* **1995**, *12*, 83–117. (b) Hanel, A. M.; Schuttel, S.; Gelb, M. H. Processive interfacial catalysis by mammalian 85-kilodalton phospholipase A_2 enzymes on product-containing vesicles: application to the determination of substrate preferences. *Biochemistry* **1993**, *32*, 5949–5958.

(2) (a) Magrioti, V.; Kokotos, G. Synthetic inhibitors of group IVA and group VIA phospholipase A_2. *Anti-Inflammatory Anti-Allergy Agents Med. Chem.* **2006**, *5* (2), 189–203. (b) Kokotos, G.; Six, D. A.; Loukas, V.; Smith, T.; Constantinou-Kokotou, V.; Hadjipavlou-Litina, D.; Kotsovolou, S.; Chiou, A.; Beltzner, C. C.; Dennis, E. A. Inhibition of group IVA cytosolic phospholipase A_2 by novel 2-oxoamides in vitro, in cells, and in vivo. *J. Med. Chem.* **2004**, *47* (14), 3615–3628.

(3) (a) Uozumi, N.; Kume, K.; Nagase, T.; Nakatani, N.; Ishii, S.; Tashiro, F.; Komagata, Y.; Maki, K.; Ikuta, K.; Ouchi, Y.; Miyazaki, J.-i.; Shimizu, T. Role of cytosolic phospholipase A_2 in allergic response and parturition. *Nature* **1997**, *390* (6660), 618–622. (b) Hegen, M.; Sun, L.; Uozumi, N.; Kume, K.; Goad, M. E.; Nickerson-Nutter, C. L.; Shimizu, T.; Clark, J. D. Cytosolic phospholipase $A_2\alpha$-deficient mice are resistant to collagen-induced arthritis. *J. Exp. Med.* **2003**, *197* (10), 1297–1302. (c) Tabuchi, S.; Uozumi, N.; Ishii, S.; Shimizu, Y.; Watanabe, T.; Shimizu, T. Mice Deficient in Cytosolic Phospholipase A_2 Are Less Susceptible to Cerebral Ischemia/Reperfusion Injury *Brain Edema XII*, Proceedings of the 12th International Symposium, Hakone, Japan, Nov 10−13, 2002; Springer: Berlin, 2003; pp 169−172. (d) Marusic, S.; Leach, M. W.; Pelker, J. W.; Azoitei, M. L.; Uozumi, N.; Cui, J.; Shen, M. W. H.; De Clercq, C. M.; Miyashiro, J. S.; Carito, B. A.; Thakker, P.; Simmons, D. L.; Leonard, J. P.; Shimizu, T.; Clark, J. D. Cytosolic phospholipase $A_2\alpha$-deficient mice are resistant to experimental autoimmune encephalomyelitis. *J. Exp. Med.* **2005**, *202* (6), 841–851. (e) Bonventre, J. V.; Huang, Z.; Taheri, M. R.; O'Leary, E.; Li, E.; Moskowitz, M. A.; Sapirstein, A. Reduced fertility and postischemic brain injury in mice deficient in cytosolic phospholipase A2. *Nature (London)* **1997**, *390* (6660), 622–625. (f) Hong, K. H.; Bonventre, J. C.; O'Leary, E.; Bonventre, J. V.; Lander, E. S. Deletion of cytosolic phospholipase A2 suppresses ApcMin-induced tumorigenesis. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98* (7), 3935–3939.

(4) (a) McKew, J. C.; Lee, K. L.; Shen, M. W. H.; Thakker, P.; Foley, M. A.; Behnke, M. L.; Hu, B.; Sum, F.-W.; Tam, S.; Hu, Y.; Chen, L.; Kirincich, S. J.; Michalak, R.; Thomason, J.; Ipek, M.; Wu, K.; Wooder, L.; Ramarao, M. K.; Murphy, E. A.; Goodwin, D. G.; Albert, L.; Xu, X.; Donahue, F.; Ku, M. S.; Keith, J.; Nickerson-Nutter, C. L.; Abraham, W. M.; William, C.; Hegen, M.; Clark, J. D. Discovery and in vitro and in vivo characterization of 4-{3-[5-chloro-2-(2-{[(3,4-dichlorobenzyl)sulfonyl]amino}ethyl)-1-(diphenylmethyl)-1*H*-indol-3-yl]propyl}benzoic acid, efipladib. *J. Med. Chem.* **2008**, *51*, 3388–3413. (b) Lee, K. L.; Behnke, M. L.; Foley, M A.; Chen, L.; Wang, W.; Vargas, R.; Nunez, J.; Tam, S.; Mollova, N.; Xu, X.; Shen, M. W. H.; Ramarao, M. K.; Goodwin, D. G.; Nickerson-Nutter, C. L.; Abraham, W. M.; Williams, C.; Clark, J. D.; McKew, J. C. Benzenesulfonamide indole inhibitors of cytosolic phospholipase $A_2\alpha$: optimization of in vitro potency and rat pharmacokinetics for oral efficacy. *Bioorg. Med. Chem.* **2008**, *16*, 1345–1358. (c) Lee, K. L.; Foley, M. A.; Chen, L.; Behnke, M. L.; Lovering, F. E.; Kirincich, S. J.; Wang, W.; Shim, J.; Tam, S.; Shen, M. W. H.; Khor, S. P.; Xu, X.; Goodwin, D. G.; Ramarao, M. K.; Nickerson-Nutter, C.; Donahue, F.; Ku, M. S.; Clark, J. D.; McKew, J. C. Discovery of ecopladib, an indole inhibitor of cytosolic phospholipase $A_2\alpha$. *J. Med. Chem.* **2007**, *50*, 1380–1400. (d) McKew, J. C.; Foley, M. A.; Thakker, P.; Behnke, M. L.; Lovering, F. E.; Sum, F.-W.; Tam, S.; Wu, K.; Shen, M. W. H.; Zhang, W.; Gonzalez, M.; Liu, S.; Mahadevan, A.; Sard, H.; Khor, S. P.; Clark, J. D. Inhibition of cytosolic phospholipase $A_2\alpha$: hit to lead optimization. *J. Med. Chem.* **2006**, *49* (1), 135–158. (e) McKew, J. C.; Lovering, F.; Clark, J. D.; Bemis, J.; Xiang, Y.; Shen, M.; Zhang, W.; Alvarez, J. C.; Joseph-McCarthy, D. Structure−activity relationships of indole cytosolic phospholipase $A_2\alpha$ inhibitors: substrate mimetics. *Bioorg. Med. Chem. Lett.* **2003**, *13* (24), 4501–4504.

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

(6) Dessen, A.; Tang, J.; Schmidt, H.; Stahl, M.; Clark, J. D.; Seehra, J.; Somers, W. S. Crystal structure of human cytosolic phospholipase A2 reveals a novel topology and catalytic mechanism. *Cell* **1999**, *97*, 349–360.

(7) (a) Lipinski, C. A. Integration of physicochemical property considerations into the design of combinatorial libraries. *Pharm. News* **2002**, *9*, 195–202. (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility

and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25.

(8) Michalak, R. S.; Helom, J. L.; Zeldis, J. Process for the Synthesis of Sulfonyl Halides and Sulfonamides from Sulfonic Acid Salts. U.S. Pat. Appl. Publ. US 2007021614 A1 20070125, 2007; 13 pp.

(9) (a) Hromatka, O.; Knollmueller, M.; Binder, D. Syntheses of 1,3-dihydro-2,1,4-benzothiadiazepines. *Monatsh. Chem.* **1969**, *100*, 872–878. (b) Griffiths, D.; Hull, R.; Seden, T. P. The chemistry of *o*-phenylenediisothiocyanate. Part 3. Studies on the syntheses of heterocyclic compounds. *J. Chem. Soc., Perkin Trans 1* **1980**, (11), 2608–2611.

(10) (a) Frankel, M.; Moses, P. Syntheses of amino alkyl sulphonic acids and their peptide analogues. *Tetrahedron* **1960**, *9*, 289–294. (b) Moe, G. R.; Sayre, L. M.; Portoghese, P. S. An explanation for the failure of aminomethanesulfonic acid to form sulfonamides. Acyl chloride-promoted generation of α-carboxamidoalkylating electrophiles. *Tetrahedron Lett.* **1981**, *22*, 537–540.

(11) Ashford, S. W.; Grega, K. C. Oxidative cleavage of 1,3-dicarbonyls to carboxylic acids with oxone. *J. Org. Chem.* **2001**, *66*, 1523–1524.

(12) (a) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. Simple, efficient catalyst system for the palladium-catalyzed amination of aryl chlorides, bromides, and triflates. *J. Org. Chem.* **2000**, *65*, 1158–1174. (b) Hartwig, J. F. Transition metal catalyzed synthesis of arylamines and aryl ethers from aryl halides and triflates: scope and mechanism. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.

(13) King, J. F.; Hawson, A.; Huston, B. L.; Danks, L. J.; Komery, J. Chlorination of heterocyclic and acyclic sulfonhydrazones. *Can. J. Chem.* **1971**, *49*, 943–955.

(14) (a) Abraham, W. M.; Ahmed, A.; Cortes, A.; Sielczak, M. W.; Hinz, W.; Bouska, J.; Lanni, C.; Bell, R. L. The 5-lipoxygenase inhibitor zileuton blocks antigen-induced late airway responses, inflammation and airway hyperresponsiveness in allergic sheep. *Eur. J. Pharmacol.* **1992**, *217* (2−3), 119–126. (b) Bell, R. L. The development of zileuton (ZYFLO) and the *N*-hydroxyurea class of 5-lipoxygenase inhibitors. *Novel Inhibitors Leukotrienes* **1999**, 235–249.

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

(16) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). *J. Med. Chem.* **1997**, *40* (9), 1347–1365.

(17) (a) Mukherjee, A.; Hale, V. G.; Borga, O.; Stein, R. Predictability of the clinical potency of NSAIDs from the preclinical pharmacodynamics in rats. *Inflammation Res.* **1996**, *45* (11), 531–540. (b) Otterness, I. G.; Bliven, M. L. *Laboratory Models for Testing Nonsteroidal Antiinflammatory Drugs*; John Wiley & Sons: New York, 1985; pp 111−251.

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