2-(4-Chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*H*]quinoline-4-carboxylic Acid (PSI-697): Identification of a Clinical Candidate from the Quinoline Salicylic Acid Series of P-Selectin Antagonists

Neelu Kaila,* Kristin Janz, Adrian Huang, Alessandro Moretto, Silvano DeBernardo, Patricia W. Bedard, Steve Tam, Valerie Clerin, James C. Keith, Jr., Desirée H. H. Tsao, Natalia Sushkova, Gray D. Shaw, Raymond T. Camphausen,† Robert G. Schaub, and Qin Wang

Chemical and Screening Sciences, Cardiovascular and Metabolic Disease, Drug Safety and Metabolism, Wyeth Research, 200 Cambridge Park Drive, Cambridge, Massachusetts 02140

Received May 26, 2006

P-selectin-PSGL-1 interaction causes rolling of leukocytes on the endothelial cell surface, which subsequently leads to firm adherence and leukocyte transmigration through the vessel wall into the surrounding tissues. P-selectin is upregulated on the surface of both platelets and endothelium in a variety of atherosclerosis-associated conditions. Consequently, inhibition of this interaction by means of a small molecule P-selectin antagonist is an attractive strategy for the treatment of atherosclerosis. High-throughput screening and subsequent analoging had led to the identification of compound **1** as the lead candidate. Herein, we report the continuation of this work and the discovery of a second-generation series, the tetrahydrobenzoquinoline salicylic acids. These compounds have improved pharmacokinetic properties, and a number of them have shown oral efficacy in mouse and rat models of atherogenesis and vascular injury. The lead **31** (**PSI-697**), is currently in clinical development for the treatment of atherothrombotic vascular events.

Introduction

Selectins are well-established therapeutic targets for the prevention and treatment of inflammatory diseases.[1−5] Several recent studies have also demonstrated a key role of selectins in atherosclerosis, with P-selectin playing the predominant role in disease.[6−9] P-selectin is found on the surface of activated platelets and endothelial cells. The ligand for P-selectin, P-selectin glycoprotein ligand 1 (PSGL-1[a]), is expressed constitutively on the surface of leukocytes, including monocytes. P-selectin-PSGL-1 interaction causes rolling of leukocytes on the endothelial cell surface, which subsequently leads to firm adherence and leukocyte transmigration through the vessel wall into the surrounding tissues. Although P-selectin is not normally expressed on the surface of unactivated cells, it is upregulated on the surface of both platelets and endothelium in a variety of atherosclerosis-associated conditions. This higher P-selectin expression on endothelium increases trafficking of leukocytes to the vessel surface and provides two stimuli to lesion growth and development. The first is the increased accumulation of the foam cell precursors (monocytes) and cells associated with lesion instability and an inflammatory state (neutrophils and lymphocytes). The second is increased accumulation of platelets, which are known to increase the myointimal proliferative state.[5,10,11] P-selectin-PSGL-1 interactions also promote the thrombotic state. Soluble P-selectin, shed from activated endothelium and activated platelets, binds PSGL-1 on leukocytes, causing the production of procoagulant microparticles, leading to thrombus growth and extension. Thus, P-selectin-PSGL-1 interactions can be expected to mediate lesion development and thrombosis. Over the past decade, numerous studies using knock-out animal models or protein therapeutics have shown that inhibiting the P-selectin-PSGL-1 interaction results in reduced atherosclerotic lesion development,[12] reduced myointimal proliferation,[13,14] and reduced venous thrombosis.[15,16] Treatment with a P-selectin inhibitor in a chronic fashion, therefore, has potential to prevent and treat atherosclerotic vascular disease.

Some selectin inhibitors have been under evaluation in clinical trials for the treatment of psoriasis, trauma, reperfusion injury, and asthma. Two small molecule inhibitors, Cylexin and bimosiamose, as well as two protein therapeutics, recombinant PSGL-Ig and humanized anti-L-selectin monoclonal antibody, have reached phase II clinical trials.[17−20] Other advanced non-carbohydrate selectin inhibitors that have shown efficacy in animal models[21] are substituted imidazole (OC229-648),[22] thiazepine pyranone (KF38789),[23] and efomycine M.[24] We recently reported[25] the identification of a series of non-carbohydrate-based quinolines as P-selectin inhibitors via high-throughput screening, using a P-selectin ELISA assay. Through SAR study we were able to significantly improve the P-selectin inhibitory activity and at the same time mitigate issues such as dihydroorotate dehydrogenase and CYP inhibitory activities.[25] The lead compound **1** showed efficacy in the rat AIA model of rheumatoid arthritis but was not taken forward due to poor bioavailability.[26] In addition, the C-2 aryl class of quinolines has been extensively studied in the past[27−29] and, therefore, patentability became a concern. Herein we report the continuation of this work and the discovery of a second-generation series, the tetrahydrobenzoquinoline salicylic acids. These compounds have improved pharmacokinetic properties, and a number of them have shown oral efficacy in mouse and rat models of atherogenesis and vascular injury. The lead, **31** (**PSI-**

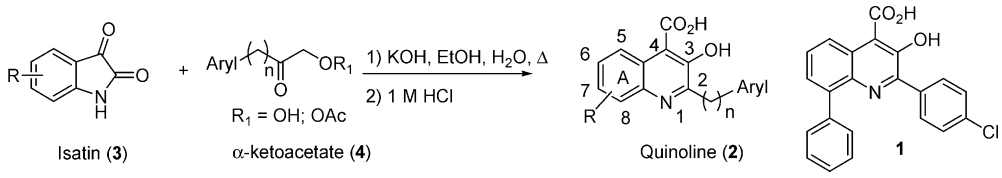
* Corresponding author. Phone: 617-665-5626. Fax: 617-665-5682. E-mail: nkaila@wyeth.com.

† Present address: Adnexus Therapeutics, Inc., MA.

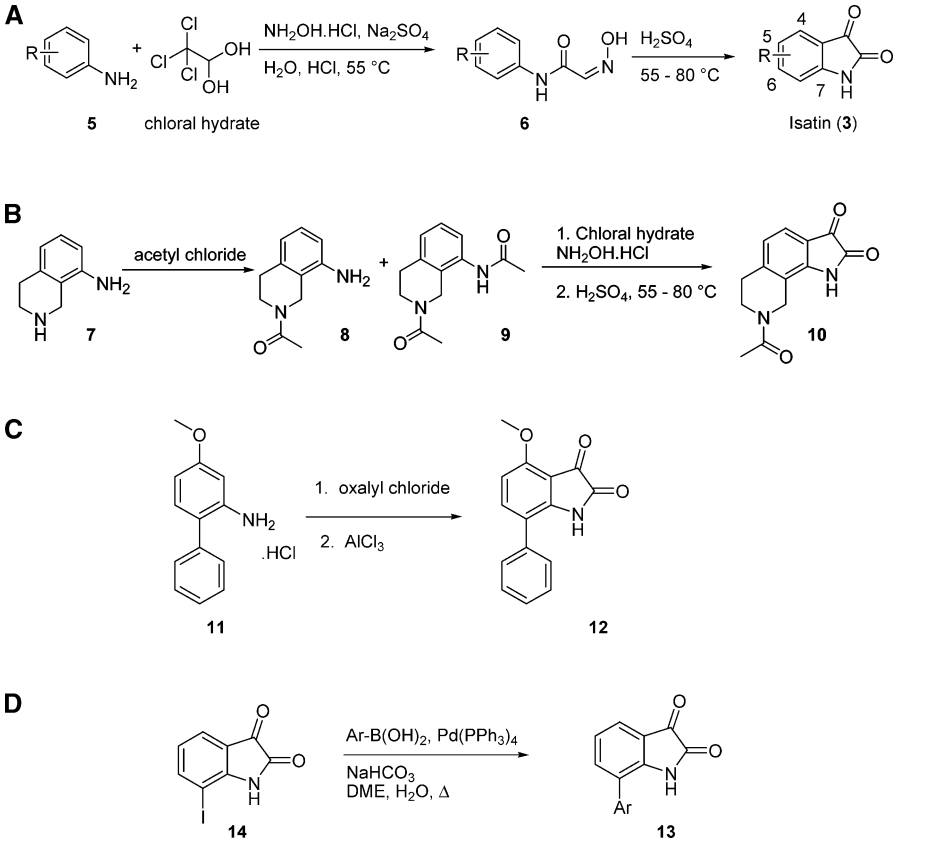
[a] Abbreviations: PSGL-1, P-selectin glycoprotein ligand-1; sLe^x, sialyl Lewis^x; SAR, structure activity relationship; STD, saturation transfer difference; PAMPA, parallel artificial membrane permeability assay; KF38789, (*E*)-3-(7-(2,4-dimethoxyphenyl)-2,3,6,7-tetrahydro-1,4-thiazepin-5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one; OC229-648, 3-(4-{4-[4-((*E*)-2-carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid; bimosiamose, 1,6-bis-[3-(3-carboxymethylphenyl)-4-(*O*-α-D-mannopyranosyl)phenyl] hexane; cylexin, a synthetic sialyl Lewis^x analogue.

10.1021/jm060631p CCC: $37.00
Published on Web 12/14/2006

Scheme 1



Scheme 2. Sandmeyer Isatin Synthesis



697),[30] is currently in clinical development for the treatment of atherothrombotic vascular events.

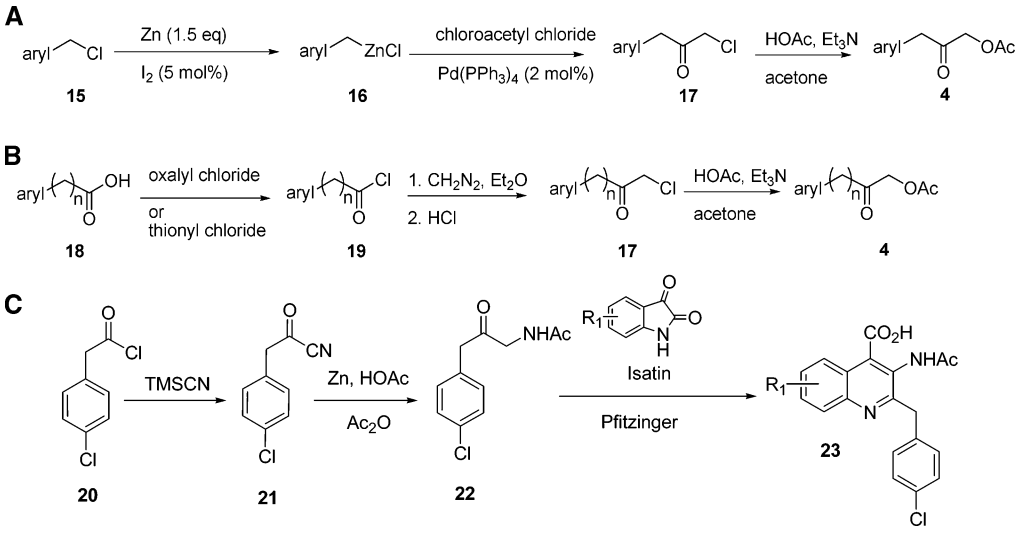
Chemistry

The target quinolines (**2**) were synthesized using the Pfitzinger reaction between an isatin (**3**) and an α-keto acetate (**4**), as described previously (Scheme 1).[25,31] The isatins **3**, were either commercially available or prepared via the Sandmeyer reaction of aniline derivatives **5** with chloral hydrate and hydroxylamine hydrochloride (Scheme 2A),[32] followed by cyclization of the resulting hydroxyiminoacetanilide intermediates **6** by heating in concentrated sulfuric acid. Some starting anilines for the Sandmeyer reaction were synthesized in house. For example, the acetyl tetrahydroisoquinoline amine **8** needed for the synthesis of isatin **10** was synthesized by the regioselective acetylation of tetrahydro-5-aminoisoquinoline **7** (Scheme 2B). In this case, addition of methylamine as a scavenger of acetyl chloride as soon as TLC analysis indicated consumption of starting material **7** was crucial for suppressing the formation of the diacetylated product **9**. Electron-rich starting materials such as biphenyl anisidine **11** gave a sulfonated byproduct under the Sandmeyer reaction. The desired product **12**, however, could be obtained by treatment of the aniline with oxalyl chloride, followed by Friedel−Crafts acylation (Scheme 2C).[33] The 7-aryl isatins **13** were prepared from the corresponding iodoisatin **14** by Suzuki coupling (Scheme 2D).

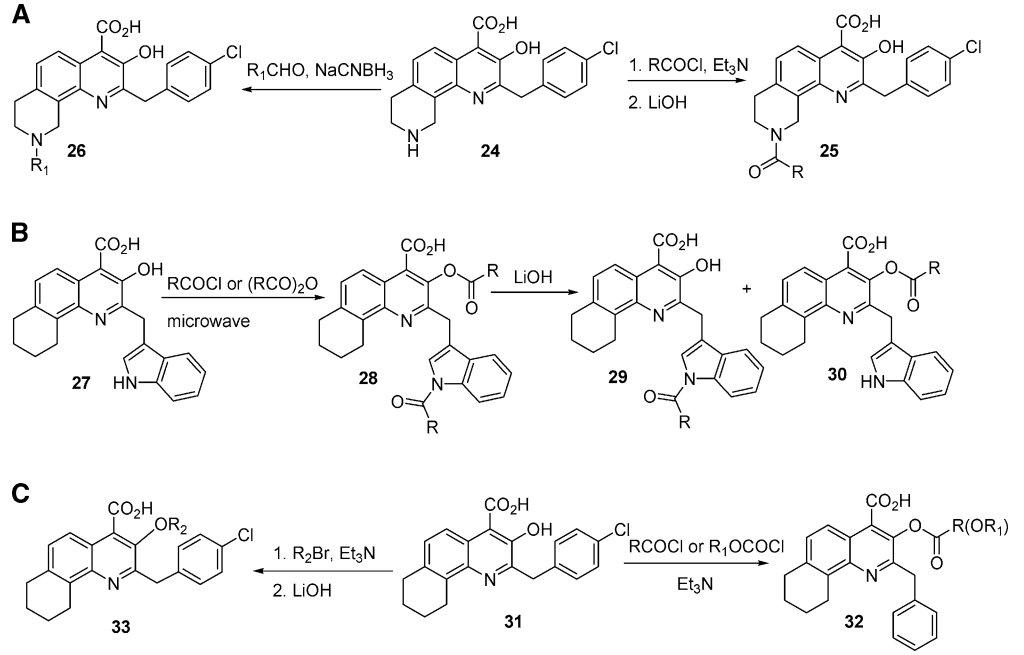
The keto acetates **4** for the Pfitzinger reaction were prepared by one of two means: (1) Pd-catalyzed coupling of arylzinc reagents (**16**) to chloroacetyl chloride,[34] followed by acetate displacement of the chloride (Scheme 3A), or (2) Arndt−Eistert homologation of an acid chloride to give chloroketones **17**, followed by acetate displacement (Scheme 3B). The two methods were found to be complementary, with the choice of method depending on commercial availability of either the aryl halide/arylzinc reagent or the arylacetic acid/acid chloride. The Pd-catalyzed methodology (Scheme 3A) did not work with any heterocyclic benzyl halides such as thiophenes, thiazoles, benzothiazoles, and pyridines. The Arndt−Eistert procedure (Scheme 3B) was somewhat more general, allowing the preparation of α-chloroketones (**17**) containing thiophene, benzothiophene, isoxazole, benzisoxazole, and carbamate-protected indole functionalities. However, isoxazoles and benzisoxazoles did not survive the harsh alkaline conditions of the Pfitzinger reaction.

The ketoacetamide **22**, required for the synthesis of the C-3 aminoquinoline derivatives (**23**), was prepared in two steps from commercially available 2-(4-chlorophenyl)acetyl chloride **20** by using a related literature procedure (Scheme 3C).[35] Treatment of **20** with trimethylsilyl cyanide gave the acyl cyanide **21**, which upon reduction with zinc in acetic acid/acetic anhydride yielded **22**.

Scheme 3



Scheme 4

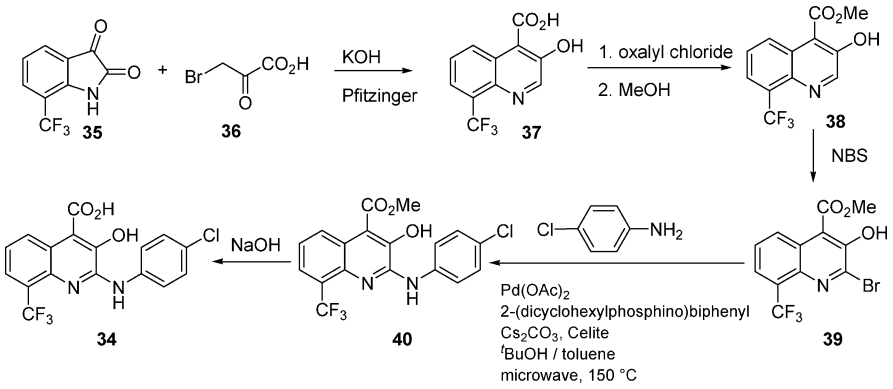


The yields for the Pfitzinger reaction ranged from 5 to 80%. The purification of the final products (Scheme 1, Tables 1−12) was not trivial due to the poor solubility of the final quinoline salicylic acids. However, the solubility of their triethylammonium salts was greatly improved. The products from the Pfitzinger reactions were generally purified either by recrystallization or by prep HPLC using triethylamine as a modifier. For further derivatization of the quinoline salicylic acids, a full protection of the salicylic acid functionality was not needed. For example, the *N*-acyl derivatives (**25**) of **24** could be obtained by peracetylation followed by selective *O*-deprotection (Scheme 4A). The *N*-alkyl derivatives (**26**) of **24** were prepared via reductive amination. The chemistry for the *N*-acylation of **27** did not work as smoothly. Microwave heating of **27** with a large excess of an acid chloride or anhydride gave the bisacylated products **28**. However, contrary to our expectations, LiOH treatment of the latter in some cases caused the amide to be hydrolyzed prior to the ester (Scheme 4B). The C-3 esters and carbonates (**32**) of **31** were prepared by treatment with a variety of acid chlorides or chloroformates in the presence of triethylamine. The C-3 ethers, **33**, were prepared in two steps from **31**, dialkylation followed by saponification of the C-4 ester (Scheme 4C).

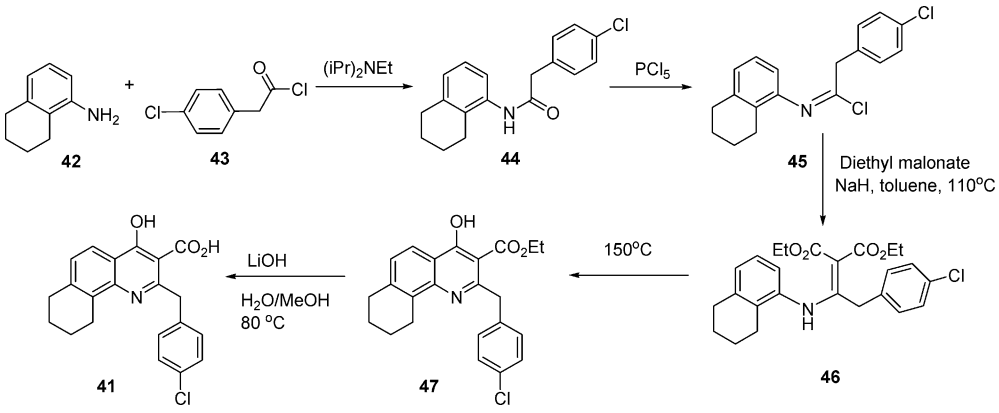
The *N*-linked derivative **34** was prepared as shown in Scheme 5. Pfitzinger reaction of 7-trifluoromethylisatin (**35**) with bromopyruvic acid (**36**) gave **37**, which after protection as a methyl ester (**38**) gave the C-2 bromo derivative **39** on bromination with NBS. Under a palladium-catalyzed amination reaction **39** gave a low yield of **40** along with a large amount of the side-product **38**. Saponification of **40** gave compound **34**.

The 3-carboxyl-4-hydroxytetrahydrobenzoquinoline **41** was prepared in an 8% overall yield from amide **44**. Heating of **44** with neat PCl_5 at 65 °C gave imidoyl chloride **45**, and treatment of the crude mixture with diethyl malonate and sodium hydride in refluxing toluene gave product **46**. Heating of compound **46** neat at 150 °C under mild vacuum overnight gave the ester **47**, which on saponification with lithium hydroxide in methanol/water at 80 °C overnight gave the target 3-carboxyl-4-hydroxyquinoline **41** (Scheme 6).

Scheme 5



Scheme 6



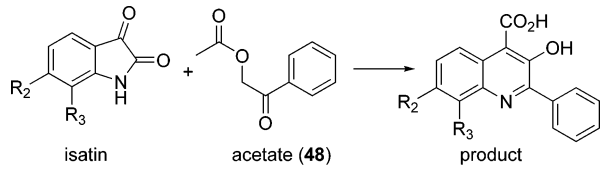
Results and Discussion

All compounds were first screened in a Biacore assay. In this assay, soluble P-selectin near the K_D concentration is flowed over immobilized PSGL-1 with and without small molecule inhibitor. The sensitivity of the Biacore instrument allows for measurement of the weak monomeric selectin interactions in real time under equilibrium flow conditions. The natural ligand sialyl Lewis^x (sLe^x) has an IC_{50} of approximately 15 mM in the Biacore assay. Therefore, compounds with $IC_{50} \leq 500$ uM were considered interesting leads. It is well-demonstrated in the literature that this high IC_{50} can translate to in vivo efficacy due to the nature of the selectin biology.[36]

In our earlier paper, we reported the SAR study and in vivo efficacy of our first lead compound **1**.[25] Further study of the C7/C8 substitution identified the tetrahydrobenzoquinoline scaffold. The C-7,8 fused ring compound **49** showed improved activity in the Biacore assay compared to the C-7,8 dimethyl (**53**) and the unsubstituted analogues (**51**; Table 1). Addition of a 1-carbon or 2-carbon linker between the quinoline ring and the C-2 phenyl ring in **49** led to a moderate improvement in activity (Table 2). On the other hand, a polar substituent on the C-2 benzyl ring had a deleterious effect (Table 3). In contrast, a small lipophillic substituent, such as a chloro group, improved bioactivity. The poor activity of the dichloro compound **71**, was probably due to the poor solubility.

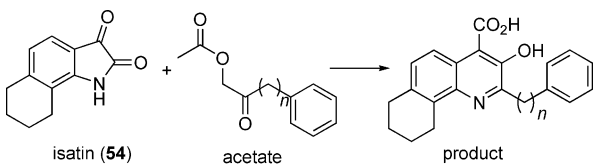
Replacement of the phenyl ring in the C-2 benzyl series with other heterocycles was acceptable (Table 4). In line with our previous observations,[25] increased lipophilicity at C-2 favored bioactivity. Thus, benzothiophene (**79**) and 5-methyl thiophene (**77**) have greater activity than the unsubstituted thiophene analogues (**73** and **75**), and the indole (**27**) and benzofuran (**82**) analogues are less-active than the benzothiophene (**79**). Further substitution at the benzothiophene ring with a lipophilic group, however, resulted in a loss of activity. Although the poor solubility of compounds **84** and **86** might have impacted the assay (Table 5). Interestingly, similar substitution on the indole compound **27** did give moderate improvement in activity due

Table 1. Tetrahydrobenzoquinolines as P-Selectin Inhibitors



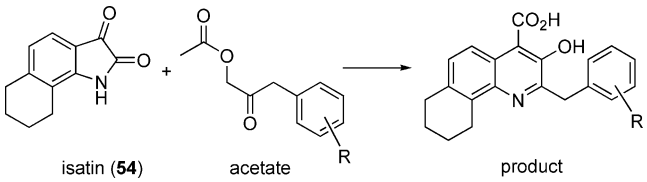
isatin	R_2	R_3	product	Biacore IC_{50}
50	H	H	**51**	6.5 mM
52	CH_3	CH_3	**53**	1.5 mM
54			**49**	550 uM

Table 2. Varying the Linker Length at the C-2 Position



acetate	*n*	product	Biacore IC_{50} (uM)
55	1	**56**	413
57	2	**58**	450

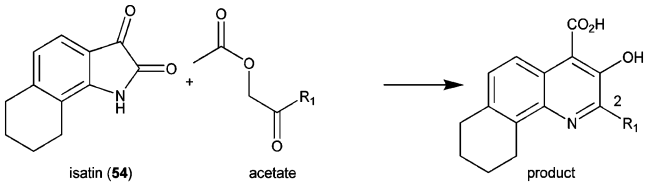
Table 3. SAR of the C-2 Benzyl Series

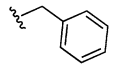
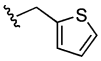
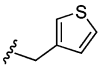
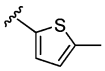
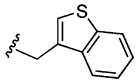
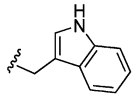
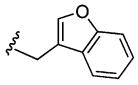


acetate	R	product	Biacore IC_{50} (μM) or % inh @ 500 μM
55	H	**56**	413
59	4-OCF_3	**60**	610
61	4-$CONH_2$	**62**	1250
61	4-CO_2H	**63**	10%
61	4-CN	**64**	500
65	4-Cl	**31**	125
66	3-Cl	**67**	138
68	2-Cl	**69**	123
70	3,4-diCl	**71**	36%[a]

[a] Compound insoluble in assay conditions.

Table 4. SAR at the C-2 Position of the Tetrahydrobenzoquinolines

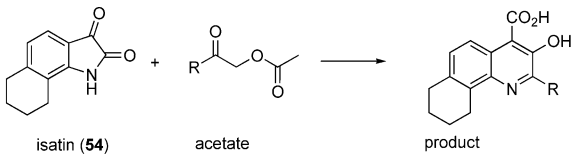


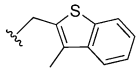
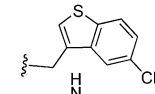
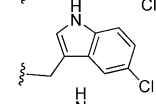
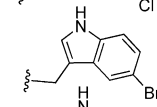
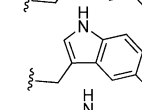
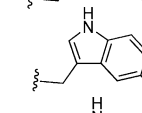
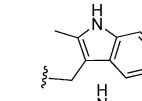
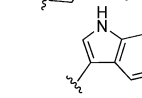
acetate	R_1	product	Biacore IC_{50} (uM)
55		**56**	413
72		**73**	413
74		**75**	475
76		**77**	200
78		**79**	100
80 (R_1 = CbzIndole)		**27**	225
81		**82**	225

to the increase in lypophilicity. As expected, incorporation of a polar carbonyl or carboxyl group onto the indole nitrogen led to a significant loss of activity (Table 6). Varying the linker length between the indole and the quinoline ring did not have an effect on bioactivity, as shown by comparing **97** to **27**.

In the second part of the study, we selected the C-2 benzyl analogue **31** to explore the SAR of the salicylic acid functionality (Table 7). Small C-3 esters or carbonates caused loss of potency whereas large esters and carbonates maintained activity. These data suggest that the C-3 hydroxy is important for activity; however, adding lipophilic groups at that position can compensate for the loss of activity caused by elimination of the hydroxyl functionality. Both large and small C-3 ethers (**108** and **109**) showed diminished activity. An amino or amide group was not

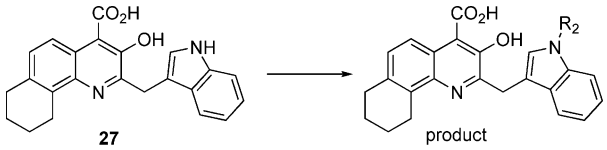
Table 5. SAR of the 2-Indolemethyl Tetrahydrobenzoquinolines

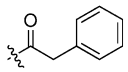
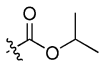


acetate	R	product	Biacore IC_{50} (uM)
83		**84**	22%@ 500 uM[a]
85		**86**	NA*
87 (X = NHCbz)		**88**	175
89 (X = NHCbz)		**90**	175
91 (X = NHCbz)		**92**	200
93 (X = NHCbz)		**94**	400
95 (X = NHCbz)		**96**	270
		**97**	225

[a] Compound insoluble in assay conditions.

Table 6. SAR of the 2-Indolemethyl Series

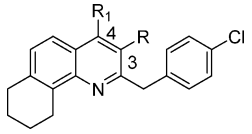


R_2	product	Biacore IC_{50} (uM)
	**98**	NA
	**99**	NA
	**100**	34% inh @ 500 mM

tolerated at the C-3 position either (**110**−**112**). Comparison of the Biacore activity of **109** to that of **113** suggests that the C-4 carboxyl group is important for activity. Switching of the acid and hydroxyl groups also decreased activity (**41**). Clearly, the position of the C-3/C-4 groups is important for P-selectin inhibition.

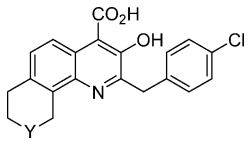
Next we studied the effect of incorporation of a nitrogen atom into the fused carbocyclic ring at C7/C8. In the C-2 benzyl series (Table 8), the introduction of this polar atom greatly diminished the P-selectin inhibitory activity, irrespective of the substituent on the nitrogen. Interestingly, SAR of other substituents at C-8 was more diverse (Table 9). Clearly, small substituents, for example, H (**123**), methyl (**125**), fluoro (**148**), gave poor activity.

Table 7. SAR of the Salicylic Acid Functionality



R_1	R	product	Biacore IC_{50} (μM) or % inh @ 250 μM
CO_2H	OH	**31**	125
CO_2H	$OCOCH_3$	**101**	545
CO_2H	$OCOC(CH_3)_3$	**102**	13%
CO_2H	OCOthiophene	**103**	175
CO_2H	$OCOC_6H_5$	**104**	190
CO_2H	OCOcyclohexyl	**105**	175
CO_2H	OCO_2CH_3	**106**	400
CO_2H	$OCO_2CH_2CH(CH_3)_2$	**107**	250
CO_2H	OCH_3	**108**	20%
CO_2H	$OCH_2C_6H_5$	**109**	390
CO_2H	NH_2	**110**	15%
CO_2H	$NHCOCH_3$	**111**	10%
CO_2H	$NHCOC_6H_5$	**112**	19%
$CO_2CH_2C_6H_5$	$OCH_2C_6H_5$	**113**	NA
OH	CO_2H	**41**	NA

Table 8. SAR of the Fused Ring in the 2-Benzyl Series

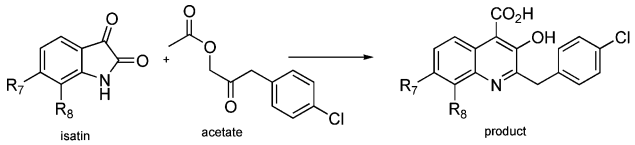


Y	product	Biacore IC_{50} (μM) or % inh @ 250 μM
CH_2	**31**	125
NH	**24**	NA
NCH_2CH_3	**114**	NA
$NCH(CH_3)_2$	**115**	NA
$NCH_2C_6H_5$	**116**	NA
$NCOCH_3$	**117**	NA
$NCOC_6H_5$	**118**	NA
$NCONH_2$	**119**	NA
$NCO_2CH_2CH_3$	**120**	NA
NSO_2CH_3	**121**	625
$NSO_2CH(CH_3)_2$	**122**	500

Increased size and lipophilicity were favored (**127**, **129**, **131**, **134**, **136**, **138**, **140**, **142**, **144**, and **146**). However, there was a limit to the degree of steric bulk that could be tolerated, as seen by the poor activity of **133**. A carboxyl group (**150**) was not tolerated. Reduction in size of the fused ring, as in **152**, diminished activity by 5-fold. Comparing with the C-8 substituted series, the C-7-substituted analogues generally had lower activity (Table 10). Moving the substituent to C-6 caused a similar loss in activity. The addition of a methoxy group to the 5-position of **138** resulted in complete loss of activity (**161**). Replacing the methylene linker between the quinoline and the phenyl ring in **134** with a nitrogen atom (**34**) improved activity, but the compound was unstable under our Biacore assay conditions.

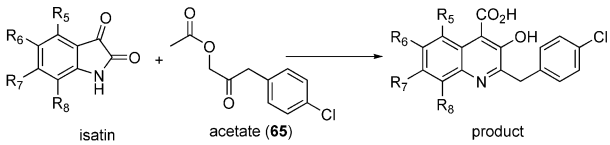
In an effort to optimize the substitution on the A ring of **27**, a library of twenty compounds was prepared (Tables 11 and 12). Initially, compounds with substitutents that had proven effective in the C-2 benzyl series were investigated. These C-2 indolylmethyl analogues were less-active than the corresponding C-2 benzyl analogues, showing that as a class this series is a few-fold weaker than the C-2 benzyl series. Compound **174**, the 5′-chloro analogue of **173**, was 10-fold more active, reiterating our earlier finding that hydrophobic substitution at the 5′-position of the indole ring improves activity.

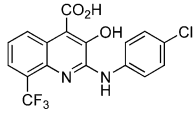
Table 9. SAR of the 8-Substituted 2-Benzyl Derivatives



isatin	R_7	R_8	product	Biacore IC_{50} (uM) or % inh. @ 500 uM
50	H	H	**123**	NA
124	H	CH_3	**125**	1000
126	H	CH_2CH_3	**127**	250
128	H	$CH(CH_3)_2$	**129**	225
130	H	$CH(CH_3)C_2H_5$	**131**	300
132	H	$C(CH_3)_3$	**133**	12%
35	H	CF_3	**134**	325
135	H	OCF_3	**136**	550
137	H		**138**	200
139	H		**140**	225
141	H		**142**	150
143	H	Br	**144**	425
145	H	Cl	**146**	715
147	H	F	**148**	12%
149	H	CO_2H	**150**	8%
151			**152**	580
54			**31**	125

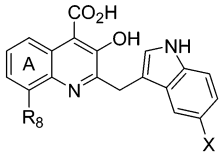
Table 10. SAR of the 6- or 7-Substituted 2-Benzyl Derivatives



isatin	R_5	R_6	R_7	R_8	product	Biacore IC_{50} (uM) or % inh @ 500uM
124	H	H	H	CH_3	**125**	1000
153	H	H	CH_3	H	**154**	12%
126	H	H	H	CH_2CH_3	**127**	250
155	H	H	CH_2CH_3	H	**156**	19%
146	H	H	H	Cl	**147**	715
157	H	H	Cl	H	**158**	900
137	H	H	H	C_6H_5	**138**	200
159	H	C_6H_5	H	H	**160**	38%
12	OCH_3	H	H	C_6H_5	**161**	NA
143	H	H	H	Br	**145**	425
162	H	Br	H	H	**163**	650
					**34**	125

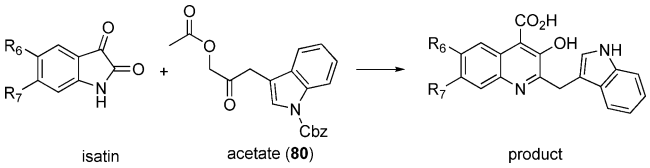
All compounds with IC_{50} values less than 200 uM (**31**, **79**, and **88**) were taken forward for evaluation in a secondary NMR assay.[37] Compound **27** was also included because of its good solubility. These compounds were evaluated for binding to P-selectin by a saturation transfer difference (STD)[38] method. The STD is widely used to confirm small molecule binding to

Table 11. SAR of the 8-Substituted 2-Indolemethyl Derivatives



R_8	X	product	Biacore IC_{50} (uM) or % inh @ 500 uM
H	H	**164**	NA
CH_3	H	**165**	11%
CH_2CH_3	H	**166**	19%
$CH(CH_3)_2$	H	**167**	415
Br	H	**168**	15%
Cl	H	**169**	NA
F	H	**170**	NA
	H	**171**	380
OCF_3	H	**172**	18%
CF_3	H	**173**	15%
CF_3	Cl	**174**	250

Table 12. SAR of the 6- or 7-Substituted 2-indolemethyl Derivatives



isatin acetate (**80**) product

isatin	R_6	R_7	product[a]
153	H	CH_3	**175**
155	H	CH_2CH_3	**176**
177	H	Br	**178**
179	CH_3	H	**180**
162	Br	H	**181**
182	F	H	**183**
184	OCF_3	H	**185**

[a] All compounds were inactive when tested at 500 μM in the Biacore assay.

biomolecules.[39] It is very efficient at detecting ligand binding to protein targets that are in fast exchange. It is a rapid experiment that uses very small amounts of protein, and it can be used for screening small libraries of compounds. There is no size limitation for the protein. In fact, the larger the protein target, the more efficient the STD signal is. STD confirmed binding to P-selectin for all four analogues, by observation of direct binding to P-selectin or by competition experiments. Two compounds (**27** and **31**) showed strong STD signals in the direct binding experiments. Direct binding by STD was not observed for **79** and **88**, likely due to poor solubility. Compound **134**, though less-potent than the four selected analogues, had good solubility in the NMR assay conditions and showed strong STD signals in the presence of P-selectin. Therefore, this compound was used as a standard and competition experiments were performed for **79** and **88** in the presence of **134**. In both cases a decrease in the STD signal for **134** was observed, confirming the binding of the analogues with P-selectin by competition with **134** (Figure 1). Competition experiments were also performed with **27** and **31**. In both cases a decrease in the STD signal for **134** was observed, suggesting that all these compounds occupy the same binding site.

Table 13. PK Parameters in Rats, Mice, and Dogs

	31			**27**		**88**
compd	rat	mouse	dog	rat	mouse	rat
PO AUC/dose (μg·hr/mL/mg)	0.62	1.5	11.67	0.607	0.218	0.096
bioavailability (%)	20	100	58	41	30	5

A one-dimensional NMR titration of compound **31** with the monomeric form of P-selectin was performed to evaluate the stoichiometery of the binding (Figure 2). Gradual line broadening for compound **31** was observed as P-selectin was added. The binding did not reach saturation. The titration was performed at 100 μM compound and protein concentrations (for practical reasons), and therefore, it was not expected that the binding would reach saturation at the last equimolar point. The titration results suggest that compound **31** titrates well with P-selectin and binds with low stoichiometry.

Compounds **27**, **31**, and **88** were taken forward, and rat PK was evaluated (Table 13).[40] Compound **88** exhibited low oral absorption. Given the low clearance and reasonable solubility (20 μg/mL at pH 7.4) for **88**, this is most likely caused by poor permeability (Pampa, 0.0×10^{-6} cm/sec). Compounds **27** and **31** exhibited good oral absorption and were, therefore, considered worthy of evaluation in the in vivo animal models.

P-selectin-mediated leukocyte rolling and tethering are critical steps for the propagation of atherothrombotic vascular events. Therefore, our first in vivo model was the intravital microscopy

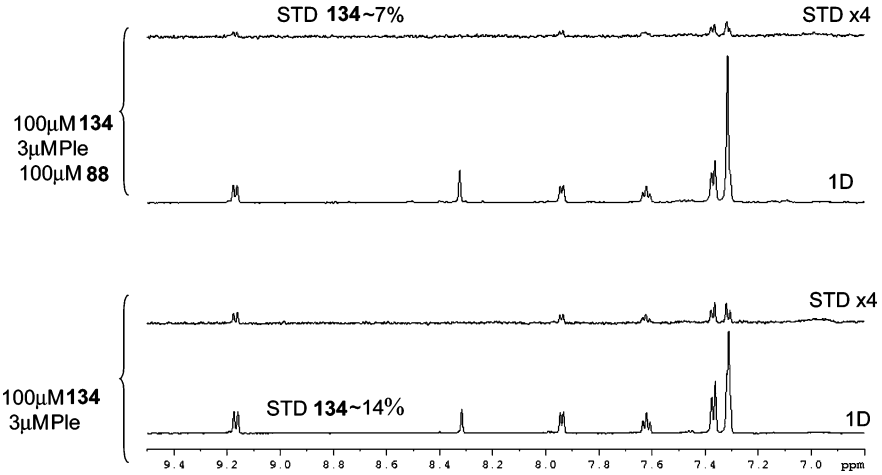


Figure 1. Binding of **134** to PLE and competition with **88**.

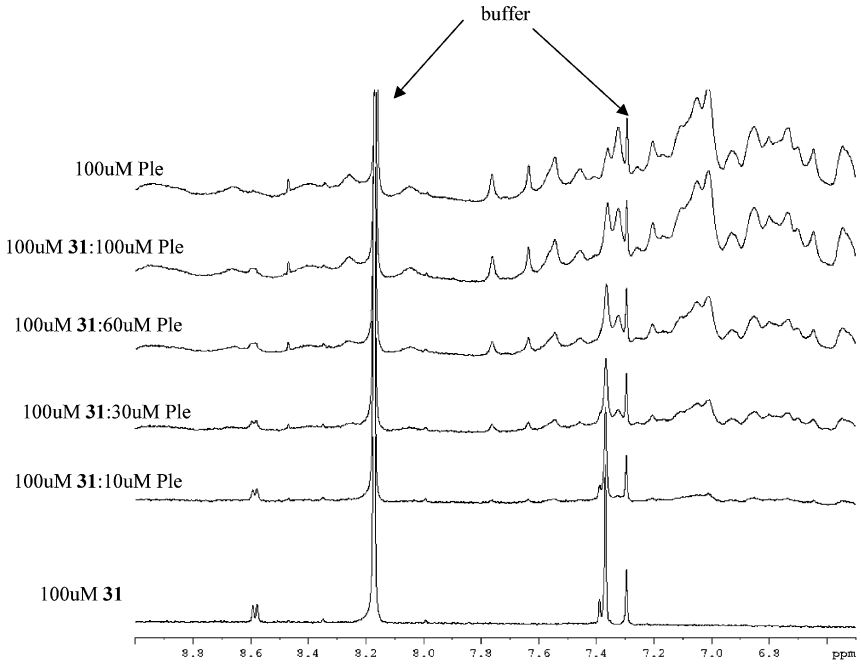


Figure 2. 1D NMR titration of compound **31** with P-selectin.

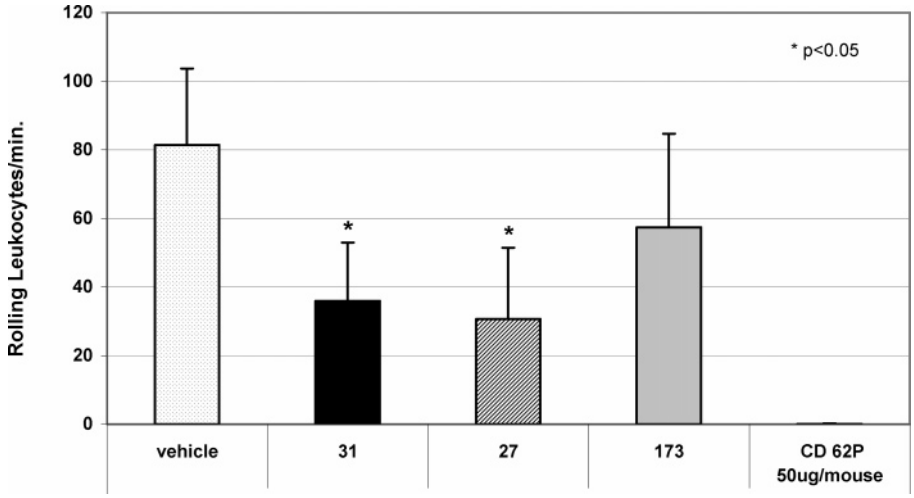
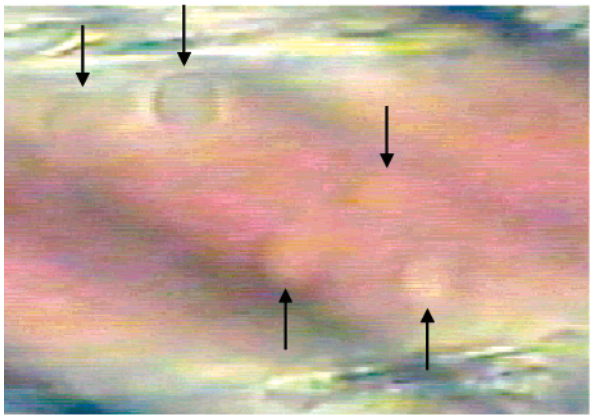


Figure 3. Efficacy of analogues **27**, **31**, and **173** in intravital microscopy rolling in mice after PO dosing at 50 mg/kg.

(IVM) leukocyte-rolling model in mice. In the literature and in our hands, the role of P-selectin in mediating leukocyte rolling has been verified using a P-selectin monoclonal antibody.[41,42] In the IVM model, the exteriorization of the mouse cremaster muscle causes up-regulation of P-selectin in postcapillary venules, which is visualized and quantitated via brightfield microscopy. Compounds were dosed as a single oral dose, formulated in methylcellulose/Tween, administered 35 min prior to measuring leukocyte rolling. Compounds **27** and **31** reduced leukocyte rolling by 62 and 56%, respectively, relative to vehicle controls at a PO dose of 50 mg/kg (Figure 3). We also evaluated one of our less-active analogues **174** at a PO dose of 50 mg/kg and observed only a 23% inhibition of leukocyte rolling, indicating a correlation between the Biacore assay and IVM efficacy. In these experiments, intravenous administration of 50 μg of our positive control, the anti-mouse CD62P (P-selectin) monoclonal antibody, showed complete inhibition of rolling. Figure 4 shows images of leukocyte rolling in cremasteric postcapillary venules in mice treated with compound **31** (Figure 4B) versus untreated (Figure 4A). This result was very encouraging because, to our knowledge, it is the first example of an orally available small molecule inhibiting P-selectin-dependent leukocyte rolling in vivo.

It is interesting to note the paradox of selectin inhibitors found in these data. Compounds **27** and **31** show efficacy in the IVM model at a C_{max} about 10-fold lower than their IC_{50} values in the Biacore assay. We have observed a similar correlation in the past.[25] The major factors that may contribute to this paradox are in vivo flow rates and selectin densities, which are difficult to precisely reproduce using in vitro systems. In addition, the shear forces, cellular interactions, and multimeric presentation of receptor and ligands seen with cell/cell interactions, in in vivo systems, differ from the monomeric protein/protein interactions measured in the Biacore biochemical assay. The former may not require the same level of receptor occupancy for effective inhibition, as required in the latter. These factors formed the basis for our rationale in pursuing micromolar selectin inhibitors. Examples of such a correlation can also been seen in the literature with the biotherapeutic rPSGL-Ig[43−45] and the small molecule-like bimosiamose: these molecules have in vitro and ex vivo IC_{50} values in the micromolar range but exhibit a markedly increased potency in vivo. Bimosiamose, which has

A.



B.

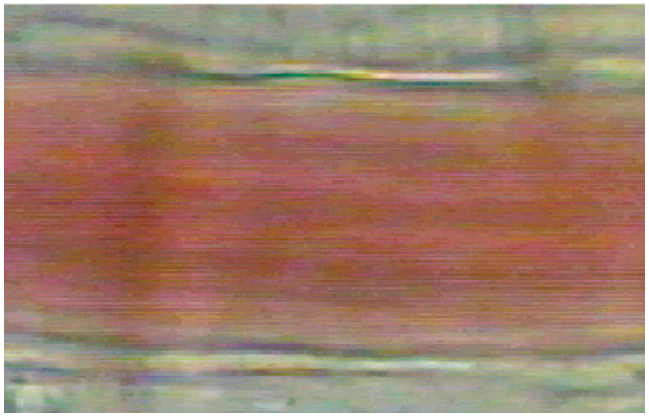


Figure 4. Intravital microscopy of cremaster venules in mice within 10 min of the initiation of surgery. Large numbers of rolling leukocytes (arrows) are seen associated with the vascular wall in vehicle treated mice (A) and no leukocytes associated with the vascular wall in **31** treated mice. Movie available in Supporting Information.

an IC_{50} of 70 μM in the P-selectin HL-60 cell assay[46] (sLe^x has an IC_{50} of 3.4 mM in this assay) has shown activity in the kidney allograft rat model[47] and allergic sheep model[48] at a dose of 10 mg/kg iv and 10 mg aerosol, respectively.

To further compare **27** and **31**, pharmacokinetic assessment of the two compounds was done in other species. Compound **31** showed superior absorption in mice compared to **27** (Table 13). Compound **31** also showed a good PK profile in a nonrodent species. The oral absorption in dogs at a dose of 15 mg/kg was high, with a bioavailability of 58% (Table 13). On the basis of its overall profile, **31** was selected as a predevelopment candidate and taken forward for evaluation in long-term animal models.

Compound **31** was evaluated in two animal models of atherogenesis and vascular injury. The first was the rat carotid balloon injury model. In this rat model of restenosis, others have demonstrated that P-selectin plays a major role in the vascular response to injury.[49−51] Sprague−Dawley rats that underwent angioplasty of the left carotid artery were dosed with vehicle or **31** at 30 mg/kg by oral gavage 1 h prior to arterial injury and once daily thereafter for 13 days. Histology of the carotid arteries showed that **31** inhibited neointimal hyperplasia by 40% at 30 mg/kg relative to the vehicle control (Figure 5).

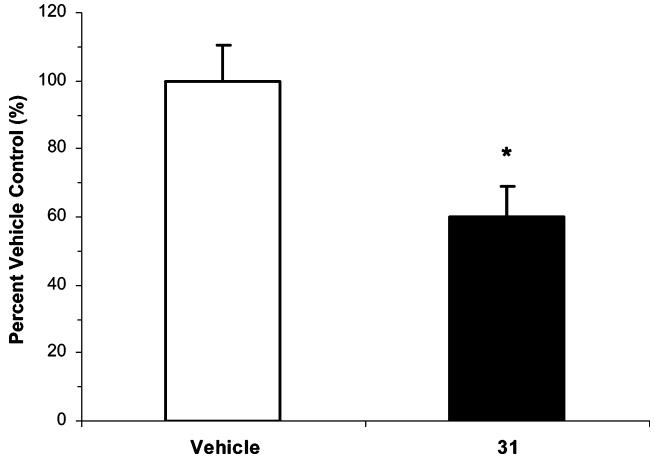


Figure 5. Efficacy of **31** in rat carotid balloon injury model. Quantitation of carotid injury, neointimal area was normalized by medical area to give intima/media ratio. *$p = 0.03$.

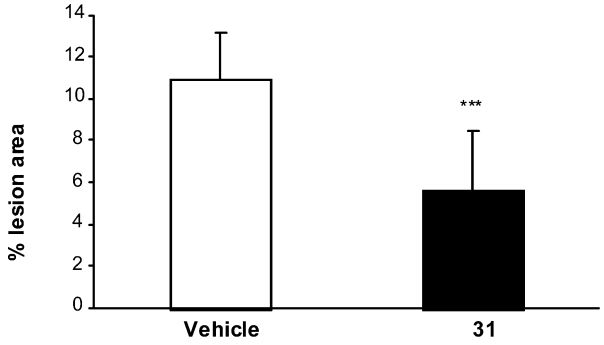


Figure 6. Efficacy of **31** in the apo E −/− mouse model. Quantitation of lesions along the aorta in animals treated with **31**. ***$p < 0.0001$.

Second was the atherogenic Apo E −/− mouse model, where an Apo E deficient mouse with a concomitant P-selectin deficiency has been shown to ameliorate disease.[52] Compound **31** was tested in this mouse model of atherosclerosis. Six-week-old male Apo E −/− mice were administered **31** at 100 mg/kg/day mixed in their normal chow for 20 weeks. Compound **31** inhibited aortic lesion surface area by 49% (Figure 6) at 100 mg/kg relative to the vehicle control. On the basis of positive data in both models, compound **31** was advanced to development track.[53,54]

In summary, we have described the structure−activity relationships of the 7,8-tetrahydrobenzo, C-2 benzyl, and C-2 indolylmethylquinolines, and our study led to the identification of development candidate **31**. Compound **31** reduced leukocyte rolling on inflamed mouse endothelium by 56% and was active in two distinct animal models of atherogenesis and vascular injury.[53,54] In addition, oral administration of **31** decreased thrombosis in a mouse model of stasis-induced venous thrombosis formation.[55] This compound has successfully completed preclinical development and is currently in Phase 1 clinical study for the treatment of atherothrombotic vascular events. To our knowledge, **31** is the first example of an orally available non-carbohydrate small molecule P-selectin inhibitor to advance to Phase 1 clinical studies.

Experimental Section

Chemistry. Reactions were run using commercially available starting materials and solvents, without further purification. Proton NMR spectra were recorded at 300 MHz on a Varian Gemini 2000 or at 400 MHz on a 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. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4 of the theoretical values. Low resolution mass spectra were obtained using a Micromass platform electrospray ionization quadrupole mass spectrometer. High resolution mass spectra were obtained using a Bruker 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. The microwave procedures were carried out with a Biotage microwave. Preparative HPLC was run using a Waters reverse phase prep HPLC with Xterra C18 5 μM, 30 × 100 mm column. The flow rate was 40 mL/min and mobile phase A was water; mobile phase B was CH_3CN; and triethylamine was used as a modifier. Purity in two solvent systems [H_2O-CH_3CN (method 1) and H_2O−MeOH (method 2)] was determined using an Agilent 1100 HPLC instrument, and all compounds analyzed were >95% pure.

Indoline-2,3-diones. General Procedure I. The hydroxyiminoacetanilide intermediate was prepared according to the procedure described by Yang et al.[32] The cyclization of this intermediate to the isatin was carried out as described by Marvel and Hiers.[32] Chloral hydrate (14.7 g, 88.8 mmol) was added to a 1 L round-bottomed flask containing a suspension of hydroxylamine hydrochloride (18.5 g, 0.266 mol), sodium sulfate (84 g, 0.59 mol), and the appropriate aniline (74.0 mmol) in 500 mL water and 25 mL 2 M aqueous hydrochloric acid. The mixture was then heated at 55 °C overnight, with stirring. After cooling to room temperature, the hydroxyiminoacetanilide could usually be collected by filtration. The solid was washed with water and dried under vacuum. To carry out the cyclization, the intermediate was added in small portions, with stirring, to a 250 mL Erlenmeyer flask containing 45 mL concentrated sulfuric acid that had been heated to 55 °C. The temperature of the reaction mixture was maintained below 70 °C during this addition. After all the hydroxyiminoacetanilide had been added, the dark-colored solution was heated at 80 °C for an additional 10 min, then cooled to room temperature, poured onto 225 mL crushed ice, and allowed to stand for 30 min. The precipitate was collected by filtration, washing three times with water, and dried under vacuum to yield indoline-2,3-dione, which was usually of sufficient purity to be used directly in the next step. Occasionally, the first step produced an oil or a sludge rather than an isolable solid. In these cases, the hydroxyiminoacetanilide was obtained by ethyl acetate extraction of the cooled reaction mixture; the ethyl acetate solution was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give a viscous oil. Cold concentrated sulfuric acid was added to this oil in a 250 mL round-bottomed flask, and the mixture was heated to 80 °C for 30 min (open to the atmosphere). The reaction was then cooled to room temperature and worked up as described above. The following isatins were commercially available: **50**, **149**, **155**, **157**, **162**, **177**, **179**, **182**, and **184**. Isatin **153** was obtained from the Wyeth compound inventory.

8-Acetyl-6,7,8,9-tetrahydro-1*H*-pyrrolo[3,2-h]isoquinoline-2,3-dione (10): 2-Acetyl-1,2,3,4-tetrahydro-8-isoquinolinamine (**8**) was prepared as follows. To a solution of 1,2,3,4-tetrahydro 5-amino-isoquinoline (2.1 g, 14.1 mmol) in 125 mL of dichloromethane and 100 mL of saturated $NaHCO_3$ (aq) at 0 °C was added acetyl chloride (1 mL, 14.1 mmol) in 25 mL of dichloromethane dropwise. The resulting mixture was stirred at 0 °C for 30 min. The organic layer was separated quickly so that the organic layer remained relatively cool. To the organic layer was immediately added methylamine hydrochloride (1 g, 14.2 mmol) and diisopropylamine (2 mL, 14.1 mmol) to scavenge the unreacted acetyl chloride. Removal of the solvent followed by flash chromatography (silica gel, ethyl acetate/hexane = 5:1) gave the desired amide **8** as a light yellow oil (a mixture of two isomers in a 2:3 ratio, 2 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04 (s, 1.2 H), 2.07 (s, 1.8 H), 2.41 (dd, J = 6.1, 6.19 Hz, 1 H), 2.52 (m, 1 H), 3.66 (dd, J = 6.1, 6.2 Hz, 2 H), 4.48 (s, 1.2 H), 4.51 (s, 0.8 H), 4.85−4.93 (br s, 2 H), 6.36 (dd, J = 7.3, 7.3 Hz, 1 H), 6.47 (d, J = 7.3 Hz, 0.6 H), 6.49 (d, J = 7.3 Hz, 0.4 H), 6.85 (d, J = 7.3 Hz, 0.6 H), 6.88 (d, J = 7.3 Hz, 0.4 H). MS (electrospray): 191 $(M + H)^+$.

Amide **8** was converted to isatin **10** using general procedure I as a mixture of two isomers 2:3 ratio. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 1.2 H), 2.10 (s, 1.8 H), 2.58 (dd, J = 5.8, 6.1 Hz, 0.8 H), 2.69 (dd, J = 5.8, 6.1 Hz, 1.2 H), 3.70 (dd, J = 6.2, 6.2 Hz, 2 H), 4.63 (s, 1.2 H), 4.69 (s, 0.8 H), 6.91 (d, J = 7.6 Hz, 0.4 H), 6.92 (d, J = 7.6 Hz, 0.6 H), 7.33 (d, J = 7.8 Hz, 0.4 H), 7.37 (d, J = 7.8 Hz, 0.6 H), 11.12 (s, 0.4 H), 11.15 (s, 0.6 H). MS (electrospray): 243 $(M - H)^-$.

7-Iodoindoline-2,3-dione (14): hydroxyiminoacetanilide, beige solid, 83%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.99 (t, J = 7.7 Hz, 1 H), 7.41 (t, 1 H), 7.63 (s, 1 H), 7.76 (dd, J = 8.1, 1.3 Hz, 1 H), 7.90 (dd, J = 7.8, 1.3 Hz, 1 H), 9.38 (s, 1 H), 12.42 (s, 1 H). MS (electrospray): 289 $(M - H)^-$. Indoline-2,3-dione: dark red powder, 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.89 (t, J = 7.7 Hz, 1 H), 7.50 (d, J = 7.3 Hz, 1 H), 7.95 (d, J = 6.8 Hz, 1 H), 11.01 (s, 1 H). MS (electrospray): 272 $(M - H)^-$.

7-(Trifluoromethyl)indoline-2,3-dione (35): reddish-brown powder, 61%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23 (t, J = 7.7 Hz, 1 H), 7.78 (d, J = 7.3 Hz, 1 H), 7.85 (d, J = 8.1 Hz, 1 H), 11.46 (s, 1 H). MS (electrospray): 214 $(M - H)^-$.

6,7-Dimethylindoline-2,3-dione[56] (52): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3 H), 2.28 (s, 3 H), 6.90 (d, J = 7.8 Hz, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 11.01 (s, 1 H).

7-Methylindoline-2,3-dione (124): orange powder, 40%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3 H), 6.99 (t, J = 7.6 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.43 (d, J = 7.6 Hz, 1 H), 11.09 (s, 1 H). MS (electrospray): 162 $(M + H)^+$.

7-Ethylindoline-2,3-dione (126): orange-brown powder, 27%; recrystallization from ethanol gave orange-red needles. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, J = 7.5 Hz, 3 H), 2.56 (q, J = 7.6 Hz, 2 H), 7.03 (t, J = 7.5 Hz, 1 H), 7.35 (d, J = 7.3 Hz, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 11.11 (s, 1 H). MS (electrospray): 176 $(M + H)^+$.

7-Isopropylindoline-2,3-dione (128): brown powder, 46%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (d, J = 6.8 Hz, 6 H), 3.04 (sep, 1 H), 7.06 (t, J = 7.7 Hz, 1 H), 7.35 (d, J = 7.3 Hz, 1 H), 7.54 (d, J = 7.3 Hz, 1 H), 11.09 (s, 1 H). MS (electrospray): 188 $(M - H)^-$.

7-*sec*-Butylindoline-2,3-dione (130): hydroxyiminoacetanilide, sticky dark brown oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.75 (t, J = 7.3 Hz, 3 H), 1.14 (d, J = 6.8 Hz, 3 H), 1.51 (m, 2 H), 2.86 (m, 1 H), 7.24 (m, 4 H), 7.68 (s, 1 H), 9.57 (s, 1 H), 12.16 (s, 1 H). MS (electrospray): 219 $(M - H)^-$. Indoline-2,3-dione, 52%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.81 (t, J = 7.3 Hz, 3 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.55 (m, 2 H), 2.83 (m, 1 H), 7.06 (t, J = 7.6 Hz, 1 H), 7.36 (d, J = 7.1 Hz, 1 H), 7.51 (d, J = 7.6 Hz, 1 H), 11.09 (s, 1 H). MS (electrospray): 202 $(M - H)^-$.

7-*tert*-Butylindoline-2,3-dione (132): Isatin was isolated by ethyl acetate extraction of the solution obtained by pouring the cooled reaction mixture onto ice; 55%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (s, 9 H), 7.04 (t, 1 H), 7.39 (d, J = 7.3 Hz, 1 H), 7.55 (dd, J = 7.8, 1.3 Hz, 1 H), 10.76 (s, 1 H). MS (electrospray): 204 $(M + H)^+$.

7-(Trifluoromethoxy)indoline-2,3-dione (135): hydroxyiminoacetanilide, lumpy brown solid, 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 (m, 1 H), 7.42 (m, 2 H), 7.75 (s, 1 H), 7.97 (dd, J = 7.8, 1.3 Hz, 1 H), 9.71 (s, 1 H), 12.39 (s, 1 H). Indoline-2,3-dione, 70%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15 (t, J = 7.8 Hz, 1 H), 7.56 (d, J = 7.3 Hz, 1 H), 7.64 (d, J = 8.3 Hz, 1 H), 11.71 (s, 1 H). MS (electrospray): 230 $(M - H)^-$.

7-Bromoindoline-2,3-dione (143): hydroxyiminoacetanilide, brown solid, 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (t, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.69 (m, 2 H), 7.91 (d, J = 8.1 Hz, 1 H), 9.46 (s, 1 H), 12.45 (s, 1 H). MS (electrospray): 241 $(M - H)^-$. Indoline-2,3-dione, reddish-brown powder, 77%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.02 (t, J = 7.8 Hz, 1 H), 7.52 (d, J =

6.6 Hz, 1 H), 7.79 (d, J = 8.1 Hz, 1 H), 11.32 (s, 1 H). MS (electrospray): 224 $(M - H)^-$.

7-Fluoroindoline-2,3-dione (147): hydroxyiminoacetanilide, 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (m, 2 H), 7.29 (m, 1 H), 7.74 (s, 1 H), 7.86 (m, 1 H), 9.81 (s, 1 H), 12.30 (s, 1 H). Indoline-2,3-dione, 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08 (ddd, 1 H), 7.38 (dt, J = 7.5, 0.8 Hz, 1 H), 7.54 (ddd, J = 10.4, 8.3, 1.0 Hz, 1 H), 11.56 (s, 1 H). MS (electrospray): 164 $(M - H)^-$.

7,8-Dihydrocyclopenta[*g*]indole-2,3(1*H*,6*H*)-dione (151): hydroxyiminoacetanilide, 66%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95−2.04 (m, 2 H), 2.80 (t, J = 7.3 Hz, 2 H), 2.88 (t, J = 7.6 Hz, 2 H), 7.05 (d, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.71 (s, 1 H), 9.49 (s, 1 H), 12.19 (s, 1 H). Indoline-2,3-dione, bright-orange solid, 5.5%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02−2.11 (quint, J = 7.5 Hz, 2 H), 2.76 (t, J = 7.5 Hz, 2 H), 2.88 (t, J = 7.5 Hz, 2 H), 6.95 (d, J = 7.6 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 1 H), 11.10 (s, 1 H).

6,7,8,9-Tetrahydro-1*H*-benzo[*g*]indole-2,3-dione (54): The hydroxyiminoacetanilide was prepared as described in general procedure I and cyclized as follows. Methanesulfonic acid was placed in a three-necked 1 L round-bottomed flask under a nitrogen atmosphere and cooled in a water bath. Hydroxyiminoacetanilide was added gradually, with vigorous stirring, keeping the temperature of the reaction mixture below 25 °C; the thick mixture was then allowed to stir at room temperature until LC-MS analysis showed complete disappearance of the hydroxyiminoacetanilide (1 h). To work up the reaction, 400 mL water was placed in a three-necked 2 L round-bottomed flask and cooled to below 8 °C. The dark red reaction mixture, a thick oil, was poured slowly into this cooled water, keeping the temperature below 25 °C. The red suspension was then stirred for 30 min at room temperature and collected by suction filtration, washing several times with freshwater, and dried giving a rust-colored powder, 73%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74 (m, 4 H), 2.50 (m, 2 H), 2.74 (t, J = 5.8 Hz, 2 H), 6.79 (d, J = 7.8 Hz, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 10.95 (s, 1 H). MS (electrospray): 202 $(M + H)^+$.

4-Methoxy-7-phenylindoline-2,3-dione (12): To a 100 mL round-bottom flask under N_2 atmosphere were added 4-methoxybiphenyl-2-amine hydrochloride (0.250 g, 1.06 mmol, 1.0 equiv) and 20 mL dichloroethane. The resulting solution was cooled to 0 °C and oxalyl chloride (0.12 mL, 1.4 mmol, 1.3 equiv) was added. The mixture was allowed to warm slowly to room temperature and stirred an additional 4 h. The mixture was then heated in an oil bath to 55 °C for 30 min. This mixture was then cooled back down to 0 °C and aluminum trichloride was added (0.184 g, 1.4 mmol, 1.3 equiv). The temperature was then increased again to 60 °C and the mixture was allowed to stir at this temperature for 3 h. After cooling to room temperature, the mixture was poured into 100 mL of water. The aqueous layer was extracted with three 50 mL portions of methylene chloride. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed to give the desired product as a red solid (0.240 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (s, 3 H), 6.70 (d, J = 8.8 Hz, 1 H), 7.30−7.45 (m, 3 H), 7.46−7.58 (m, 3 H), 7.80 (s, 1 H). MS (electrospray): 254 $(M + H)^+$.

Arylindoline-2,3-diones. General Procedure II. The procedure described by Lisowski et al. was followed.[57] To a 1 L three-necked round-bottomed flask fitted with a reflux condenser were added iodoindoline-2,3-dione (**14**, 2.0 g, 7.33 mmol) and tetrakis-[triphenylphosphine]palladium (0.424 g, 0.367 mmol), followed by 225 mL of 1,2-dimethoxyethane. The atmosphere in the reaction vessel was made inert by opening to vacuum and then to a positive pressure of nitrogen (3×). Arylboronic acid (8.06 mmol) and a solution of sodium bicarbonate (1.23 g, 14.7 mmol) in 225 mL of water were added, and the evacuation/nitrogen procedure was repeated one more time. The reaction mixture was then refluxed until TLC showed complete disappearance of iodoindoline-2,3-dione (1−2 h). After cooling to room temperature, the 1,2-dimethoxyethane was removed under reduced pressure. The residue was diluted with 1 M aqueous hydrochloric acid and extracted into ethyl acetate (3×). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give the crude arylindoline-2,3-dione.

7-Phenylindoline-2,3-dione (137): purified by flash chromatography over silica gel (1% ethyl acetate in dichloromethane), orange needlelike crystals, 74%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18 (t, J = 7.6 Hz, 1 H), 7.48 (m, 6 H), 7.59 (d, J = 8.8 Hz, 1 H), 10.91 (s, 1 H). MS (electrospray): 222 $(M - H)^-$.

7-(Thiophen-3-yl)indoline-2,3-dione (139): purified by flash chromatography over silica gel (3% ethyl acetate in dichloromethane), bright red crystalline material, 54%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15 (t, 1 H), 7.36 (dd, J = 4.9, 1.4 Hz, 1 H), 7.50 (dt, J = 7.3, 1.0 Hz, 1 H), 7.68 (d, J = 1.5 Hz, 1 H), 7.71 (m, 2 H), 7.75 (dd, J = 2.9, 1.4 Hz, 1 H), 10.86 (s, 1 H). MS (electrospray): 228 $(M - H)^-$.

7-(Furan-3-yl)indoline-2,3-dione (141): purified by flash chromatography over silica gel (3% ethyl acetate in dichloromethane), 54%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.90 (dd, J = 1.9, 0.9 Hz, 1 H), 7.14 (t, 1 H), 7.48 (dt, J = 7.3, 1.0 Hz, 1 H), 7.72 (dd, J = 7.8, 1.3 Hz, 1 H), 7.83 (t, 1 H), 8.12 (t, 1 H), 10.76 (s, 1 H). MS (electrospray): 212 $(M - H)^-$.

5-Phenylindoline-2,3-dione (159): purified by flash chromatography over silica gel (3% ethyl acetate in dichloromethane), 45%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.01 (d, J = 8.1 Hz, 1 H), 7.36 (tt, 1 H), 7.63−7.68 (m, 2 H), 7.77 (d, J = 2.0 Hz, 1 H), 7.91 (dd, J = 8.3, 2.0 Hz, 1 H), 11.13 (s, 1 H). MS (electrospray): 222 $(M - H)^-$.

Benzyloxycarbonyl-indolylacetic Acids. General Procedure III. In a flame-dried two-necked 100 mL round-bottomed flask, under nitrogen, the appropriately substituted 2-(1*H*-indol-3-yl)acetic acid (5.71 mmol) was taken up in 10 mL of anhydrous THF and cooled to −78 °C. A 1.0 M THF solution of lithium bis-(trimethylsilyl)amide (12.6 mL, 12.6 mmol) was added dropwise via syringe, and the mixture was allowed to stir for 30 min at −78 °C. Benzyl chloroformate (0.90 mL, 1.1 g, 6.3 mmol) was then added dropwise via syringe, and the reaction was stirred for 1 h. It was then quenched by the addition of 2 M hydrochloric acid and partitioned between 2 M hydrochloric acid and ethyl acetate, extracting the aqueous layer with additional ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated.

Benzyl Chloromethyl Ketones. General Procedure IV. Method A: The acid chloride was first prepared in situ from the corresponding carboxylic acid. Acid (17.6 mmol) was taken up in anhydrous tetrahydrofuran in a 100 mL round-bottomed flask fitted with a rubber septum, 15 drops of anhydrous *N*,*N*-dimethylformamide were added, and the solution was cooled in an ice water bath, with stirring. The septum was pierced with an 18 G needle to vent evolved gases, and oxalyl chloride (1.7 mL, 2.5 g, 19 mmol) was then added dropwise via syringe. Vigorous gas evolution ensued. The ice bath was removed, and the reaction mixture was allowed to stir for 1 h. Meanwhile, a 1 L Erlenmeyer flask, inspected to ensure that it was free from cracks and chips, was clamped securely so that it was immersed in an ice water bath resting on a magnetic stir plate. A stir bar was placed in the flask, and 46.5 mL of diazomethane in ether (0.57 mmol/mL)[58] was added. With gentle stirring, the freshly prepared THF solution of the acid chloride was added slowly from an addition funnel suspended above the Erlenmeyer flask, over the course of 1 h. The reaction mixture was then allowed to stir 4 h or overnight, loosely covered with aluminum foil, and slowly warmed to room temperature. It was then cooled once again by immersion in a fresh ice bath, and a slow stream of dry hydrogen chloride gas was bubbled through until vigorous gas evolution ceased. The mixture was allowed to stir for 1 h, slowly warming, then poured into 85 mL of ice water in a beaker, rinsing the flask with ether. The contents of the beaker were stirred for 20 min until all the ice had melted, then extracted into ether (2 × 110 mL). The combined ether extracts were washed successively with 5% sodium carbonate (85 mL) and brine (75 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated. **Method B:** The organozinc reagent was either purchased from Aldrich or

was generated as described by Huo.[59] In a flame-dried 25 mL two-necked round-bottomed flask, under an inert atmosphere, iodine (65 mg, 0.26 mmol) was taken up in 6 mL of anhydrous *N*,*N*-dimethylacetamide. Zinc dust (0.502 g, 7.67 mmol) was added, and the suspension was stirred until the red color of the iodine disappeared. The appropriate benzyl halide (5.1 mmol) was then added via syringe, and the mixture was heated at 80 °C until the TLC of a hydrolyzed aliquot showed that it had been consumed. The reaction vessel was placed in a water bath to cool it, and Pd(PPh_3)$_4$ (0.118 g, 0.102 mmol) was added, followed by dropwise addition, via syringe, of chloroacetyl chloride (0.61 mL, 0.87 g, 7.7 mmol). The brown suspension was allowed to stir overnight at room temperature. To work up the reaction, 12 mL of 1 M hydrochloric acid was added, and the mixture was extracted into ethyl acetate (4 × 12 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated.

Acetoxymethyl Benzyl Ketones. General Procedure V. Benzyl chloromethyl ketone (55.6 mmol) was taken up in acetone and cooled in an ice bath. Acetic acid (6.4 mL, 6.7 g, 0.11 mol) was added, and then triethylamine (15.5 mL, 11.2 g, 0.111 mol) was added dropwise. The ice bath was removed, and the reaction mixture was allowed to stir overnight at room temperature. It was then filtered to remove the white precipitate of triethylammonium chloride, washing with acetone, and the filtrate was evaporated and partitioned between ethyl acetate and brine. The aqueous layer was extracted with additional ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated.

Acetate **48** was commercially available and acetate **76** was available from the Wyeth compound inventory.

2-Oxo-3-phenylpropyl Acetate (55): 1-chloro-3-phenylpropan-2-one was prepared using general procedure IV, method B. The crude product was then converted to **55** using general procedure V. Purification was done using flash chromatography (ethyl acetate−hexanes) to give **55** in 25% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3 H), 3.80 (s, 2 H), 4.85 (s, 2 H), 7.07−7.41 (m, 5 H).

2-Oxo-4-phenylbutyl Acetate (57): 1-chloro-4-phenylbutan-2-one was prepared using general procedure IV, method B. The crude product was then converted to **57** using general procedure V. Purification was done using flash chromatography (ethyl acetate−hexanes) to give **57** in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3 H), 2.68 (t, J = 7.7 Hz, 2 H), 2.87 (t, J = 7.6 Hz, 2 H), 4.55 (s, 2 H), 7.10−7.24 (m, 5 H).

2-Oxo-3-(4-(trifluoromethoxy)phenyl)propyl Acetate (59): 1-Chloro-3-(4-trifluoromethoxy phenyl)propan2-one was prepared using general procedure IV, method A, giving a colorless oil, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 2 H), 4.12 (s, 2 H), 7.18 (m, J = 22.0 Hz, 4 H).

1-Chloro-3-(4-trifluoromethoxy phenyl)propan2-one was converted to **59** using general procedure V. The residue was crystallized from ether and hexanes to afford **59** in 42% yield as colorless flakes. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.75 (s, 2 H), 4.71 (s, 2 H), 7.23 (m, 4 H).

3-(4-Cyanophenyl)-2-oxopropyl Acetate (61): 4-(3-chloro-2-oxopropyl)benzonitrile was prepared using general procedure IV, method B. The crude product was then converted to **61** using general procedure V. Purification was done using flash chromatography (ethyl acetate−hexanes) to give **61** in 20% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3 H), 3.96 (s, 2 H), 4.88 (s, 2 H), 7.40 (d, J = 8.3 Hz, 2 H), 7.76−7.82 (d, J = 8.3 Hz, 2 H).

3-(4-Chlorophenyl)-2-oxopropyl Acetate (65): 1-Chloro-3-(4-chlorophenyl)propan-2-one was prepared using general procedure IV, method A, giving an off-white solid, 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 2 H), 4.13 (s, 2 H), 7.18 (dt, J = 8.8, 2.5 Hz, 2 H), 7.34 (dt, J = 8.8, 2.5 Hz, 2 H).

In a three-necked 1 L round-bottomed flask fitted with a reflux condenser, 1-chloro-3-(4-chlorophenyl)propan-2-one (8.14 g, 40.1 mmol) was taken up in 85 mL of ethanol and heated to reflux. Acetic acid (4.2 mL) was added, followed by a solution of cesium acetate (8.47 g, 44.1 mmol) in 45 mL of water. The solution was then refluxed until TLC analysis (20% ethyl acetate in hexanes, cerium ammonium molybdate staining) showed complete consumption of the chloride (3 h). The mixture was then cooled, and ethanol was removed under reduced pressure. The aqueous mixture left behind was partitioned between 210 mL of cold saturated sodium bicarbonate and 340 mL of ethyl acetate. The aqueous layer was extracted with a second 340 mL portion of ethyl acetate, and each organic extract was washed with 340 mL of brine. The extracts were then combined, dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by flash chromatography over silica gel (20% ethyl acetate in hexanes), 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 3.73 (s, 2 H), 4.71 (s, 2 H), 7.16 (dt, J = 8.8, 2.5 Hz, 2 H), 7.33 (dt, J = 8.8, 2.5 Hz, 2 H).

3-(3-Chlorophenyl)-2-oxopropyl Acetate (66): 1-Chloro-3-(3-chlorophenyl)propan-2-one was prepared using general procedure IV, method B. The crude product, a brown oil, was directly subjected to general procedure V and then purified by flash chromatography over silica gel (20% ethyl acetate in hexanes), 46% yield from 3-chlorobenzylzinc chloride. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.72 (s, 2 H), 4.70 (s, 2 H), 7.08−7.12 (m, 1 H), 7.22 (s, 1 H), 7.26−7.29 (m, 2 H). MS (electrospray): 227 $(M + H)^+$.

3-(2-Chlorophenyl)-2-oxopropyl Acetate (68): 1-Chloro-3-(2-chlorophenyl)propan-2-one was prepared using general procedure IV, method B, and purified by flash chromatography over silica gel (10% ethyl acetate in hexanes), 22%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (s, 2 H), 4.19 (s, 2 H), 7.21−7.29 (m, 3 H), 7.38−7.42 (m, 1 H).

1-Chloro-3-(2-chlorophenyl)propan-2-one was converted to compound **68** using general procedure V and purified by flash chromatography over silica gel (5−40% ethyl acetate in hexanes), 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.88 (s, 2 H), 4.75 (s, 2 H), 7.23−7.28 (m, 3 H), 7.40 (ddd, 1 H).

3-(3,4-Dichlorophenyl)-2-oxopropyl Acetate (70): 1-Chloro-3-(3,4-dichlorophenyl)propan-2-one was prepared using general procedure IV, method B, and purified by flash chromatography over silica gel (1−30% ethyl acetate in hexanes), 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 2 H), 4.13 (s, 2 H), 7.06 (dd, J = 8.2, 2.2 Hz, 1 H), 7.33 (d, J = 2.0 Hz, 1 H), 7.42 (d, J = 8.3 Hz, 1 H).

1-Chloro-3-(3,4-dichlorophenyl)propan-2-one was converted to compound **70** using general procedure V. Purified by flash chromatography over silica gel (10−30% ethyl acetate in hexanes), 33%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 3.71 (s, 2 H), 4.71 (s, 2 H), 7.05 (dd, J = 8.2, 2.2 Hz, 1 H), 7.32 (d, J = 2.0 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H).

2-Oxo-3-(thiophen-2-yl)propyl Acetate (72): 1-Chloro-3-(thiophen-2-yl)propan-2-one was prepared using general procedure IV, method A. Commercially available 2-thiopheneacetyl chloride was taken up in ether and added to the ethereal diazomethane solution, as described above. The chloromethyl ketone product had to be stored under nitrogen at −20 °C or it would turn into an intractable black solid. Purification by flash chromatography over silica gel (5% ethyl acetate in hexanes) gave a yellow oil, 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (d, J = 0.8 Hz, 2 H), 4.17 (s, 2 H), 6.93−6.96 (m, 1 H), 7.00 (dd, J = 5.2, 3.4 Hz, 1 H), 7.26 (dd, J = 5.1, 1.3 Hz, 1 H).

1-Chloro-3-(thiophen-2-yl)propan-2-one was converted to compound **72**, purified by flash chromatography over silica gel (10−40% ethyl acetate in hexanes), orange oil, 13%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 3.95 (s, 2 H), 4.74 (s, 2 H), 6.93 (dq, J = 3.4, 1.0 Hz, 1 H), 6.99 (dd, J = 5.2, 3.4 Hz, 1 H), 7.25 (dd, J = 5.1, 1.3 Hz, 1 H).

2-Oxo-3-(thiophen-3-yl)propyl Acetate (74): 1-Chloro-3-(thiophen-3-yl)propan-2-one was prepared using general procedure IV, method A, producing a brown oil solidifying to a waxy, golden-brown solid, 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 2 H), 4.13 (s, 2 H), 6.99 (d, J = 5.1 Hz, 1 H), 7.16 (d, J = 2.3 Hz, 1 H), 7.33 (dd, J = 4.9, 2.9 Hz, 1 H). MS (electrospray): 173 $(M - H)^-$.

1-Chloro-3-(thiophen-3-yl)propan-2-one was converted to **74** using general procedure V and purified by flash chromatography over silica gel (20% ethyl acetate in hexanes), producing a golden-yellow oil, 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.77 (s, 2 H), 4.70 (s, 2 H), 6.98 (dd, J = 4.8, 1.3 Hz, 1 H), 7.14 (d, J = 1.8 Hz, 1 H), 7.32 (dd, J = 4.9, 2.9 Hz, 1 H). MS (electrospray): 199 $(M + H)^+$.

3-(Benzo[*b*]thiophen-3-yl)-2-oxopropyl Acetate (78): 1-(Benzo[*b*]thiophen-3-yl)-3-chloropropan-2-one was prepared using procedure IV, method A. The acid chloride was prepared by stirring the acid overnight with 16 equivalents of thionyl chloride; the thionyl chloride was removed by evaporation, azeotroping twice with toluene, and the crude acid chloride was taken up in ether and added to the ethereal diazomethane solution, as described above, and purified by flash chromatography over silica gel (2−30% ethyl acetate in hexanes), 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (s, 2 H), 4.14 (d, J = 1.0 Hz, 2 H), 7.36−7.44 (m, 3 H), 7.67−7.71 (m, 1 H), 7.87−7.90 (m, 1 H).

1-(Benzo[*b*]thiophen-3-yl)-3-chloropropan-2-one was converted to compound **78** using general procedure V and purified by flash chromatography over silica gel (10−40% ethyl acetate in hexanes), 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3 H), 3.98 (d, J = 0.8 Hz, 2 H), 4.71 (s, 2 H), 7.35 (s, 1 H), 7.36−7.44 (m, 2 H), 7.66−7.70 (m, 1 H), 7.86−7.90 (m, 1 H).

Benzyl 3-(3-acetoxy-2-oxopropyl)-1*H*-indole-1-carboxylate (80): 2-(1-(Benzyloxycarbonyl)-1*H*-indol-3-yl)acetic acid was prepared using general procedure III, producing a white solid with a pinkish tinge, 86%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 2 H), 5.47 (s, 2 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.32−7.47 (m, 4 H), 7.52−7.60 (m, 3 H), 7.68 (s, 1 H), 8.08 (d, J = 8.1 Hz, 1 H), 12.43 (s, 1 H). HRMS (ESI^+) calcd for $C_{18}H_{16}NO_4$ (MH^+), 310.1074; found, 310.1080.

2-(1-(Benzyloxycarbonyl)-1*H*-indol-3-yl)acetic acid was converted to benzyl 3-(3-chloro-2-oxopropyl)-1*H*-indole-1-carboxylate using general procedure IV, method A, and purified by flash chromatography over silica gel (15−20% ethyl acetate in hexanes), 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (d, J = 1.0 Hz, 2 H), 4.15 (s, 2 H), 5.45 (s, 2 H), 7.28 (d, J = 7.3 Hz, 1 H), 7.32−7.51 (m, 7 H), 7.63 (s, 1 H), 8.19 (br s, 1 H). HRMS (ESI^+) calcd for $C_{19}H_{17}ClNO_3$ (MH^+), 342.0892; found, 342.0900

Benzyl 3-(3-chloro-2-oxopropyl)-1*H*-indole-1-carboxylate was converted to **80** using procedure V and purified by flash chromatography over silica gel (20−30% ethyl acetate in hexanes), producing a viscous yellow-orange oil that partially solidifies upon refrigeration, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3 H), 3.81 (d, J = 0.8 Hz, 2 H), 4.73 (s, 2 H), 5.45 (s, 2 H), 7.24−7.51 (m, 8 H), 7.62 (s, 1 H), 8.18 (br s, 1 H). HRMS (ESI^+) calcd for $C_{21}H_{20}NO_5$ (MH^+), 366.1336; found, 366.1353.

3-(Benzofuran-3-yl)-2-oxopropyl Acetate (81): In a 20 mL microwave vial, benzofuran-3-(2*H*)-one (1.00 g, 7.45 mmol) and (carbethoxymethylene)triphenylphosphorane (3.12 g, 8.95 mmol) were taken up in 12 mL of toluene and 4 mL of *o*-dichlorobenzene. The vial was crimp-sealed and heated in a microwave cavity for 20 min at 210 °C until TLC analysis (10% ethyl acetate in hexanes) showed nearly complete consumption of the ketone. The reaction mixture was then evaporated, and the residue was extracted into boiling hexanes. Evaporation of the hexane extract gave a crude product that was purified by flash chromatography over silica gel (5−25% ethyl acetate in hexanes) to give ethyl 2-(benzofuran-3-yl)acetate as a bright red-orange oil, 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 3 H), 3.70 (d, J = 1.0 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 7.22−7.33 (m, 2 H), 7.46−7.49 (m, 1 H), 7.55−7.59 (m, 1 H), 7.63 (t, J = 1.0 Hz, 1 H).

Ethyl 2-(benzofuran-3-yl)acetate (1.86 g, 9.12 mmol) was taken up in 40 mL of ethanol and 20 mL of 10% aqueous potassium hydroxide and refluxed for 1 h. The reaction mixture was then cooled and partitioned between ethyl acetate and 2 M aqueous hydrochloric acid; the aqueous layer was extracted with additional ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 2-(benzofuran-3-yl)acetic acid as an orange-tinted, off-white solid, 98%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 2 H), 7.26 (td, J = 7.3, 0.8 Hz, 1 H), 7.32 (td, J = 7.7, 1.5 Hz, 1 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.60 (d, J = 7.1 Hz, 1 H), 7.89 (s, 1 H), 12.46 (s, 1 H). MS (electrospray): 175 $(M - H)^-$.

2-(Benzofuran-3-yl)acetic acid was converted to 1-(benzofuran-3-yl)-3-chloropropan-2-one using general procedure IV, method A, producing a brown oil, 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (d, J = 1.0 Hz, 2 H), 4.17 (s, 2 H), 7.24−7.29 (m, 1 H), 7.33 (td, J = 7.8, 1.4 Hz, 1 H), 7.49 (ddd, 2 H), 7.66 (s, 1 H).

1-(Benzofuran-3-yl)-3-chloropropan-2-one was converted to compound **81** using general procedure V and purified by flash chromatography over silica gel (5−50% ethyl acetate in hexanes), producing a yellow oil, 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 3.82 (d, J = 1.0 Hz, 2 H), 4.76 (s, 2 H), 7.24−7.35 (m, 2 H), 7.47−7.51 (m, 2 H), 7.64 (s, 1 H).

3-(3-Methylbenzo[*b*]thiophen-2-yl)-2-oxopropyl Acetate (83): 1-Chloro-3-(3-methylbenzo[*b*]thiophen-2-yl)propan-2-one was prepared using general procedure IV, method A, and purified by flash chromatography over silica gel (10% ethyl acetate in hexanes), stored at −20 °C under nitrogen, 26%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3 H), 4.13 (s, 2 H), 4.17 (s, 2 H), 7.31−7.42 (m, 2 H), 7.67 (d, J = 7.6 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H).

1-Chloro-3-(3-methylbenzo[*b*]thiophen-2-yl)propan-2-one was converted to **85** using general procedure V and purified by flash chromatography over silica gel (16−36% ethyl acetate in hexanes), 13%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3 H), 2.35 (s, 3 H), 3.97 (s, 2 H), 4.73 (s, 2 H), 7.33 (td, J = 7.5, 1.4 Hz, 1 H), 7.39 (td, J = 7.6, 1.3 Hz, 1 H), 7.64−7.68 (m, 1 H), 7.78 (dt, J = 7.8, 0.6 Hz, 1 H).

3-(5-Chlorobenzo[*b*]thiophen-3-yl)-2-oxopropyl Acetate (85): 1-Chloro-3-(5-chlorobenzo[*b*]thiophen-3-yl)propan-2-one was prepared using general procedure IV, method A, producing a light golden-yellow solid, 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (s, 2 H), 4.15 (s, 2 H), 7.35 (dd, J = 8.6, 2.0 Hz, 1 H), 7.43 (s, 1 H), 7.65 (d, J = 2.0 Hz, 1 H), 7.79 (d, J = 8.6 Hz, 1 H). MS (electrospray): 257 $(M - H)^-$.

1-Chloro-3-(5-chlorobenzo[*b*]thiophen-3-yl)propan-2-one was converted to **85** using general procedure V and purified by flash chromatography over silica gel (20% ethyl acetate in hexanes), 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.94 (d, J = 1.0 Hz, 2 H), 4.73 (s, 2 H), 7.34 (ddd, J = 8.6, 2.0, 0.5 Hz, 1 H), 7.41 (s, 1 H), 7.65 (dd, J = 2.0, 0.5 Hz, 1 H), 7.78 (dd, J = 8.6, 0.5 Hz, 1 H). MS (electrospray): 283 $(M + H)^+$.

Benzyl 3-(3-Acetoxy-2-oxopropyl)-5-chloro-1*H*-indole-1-carboxylate (87): 2-(1-(Benzyloxycarbonyl)-5-chloro-1*H*-indol-3-yl)-acetic acid was prepared using general procedure III. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (d, J = 1.0 Hz, 2 H), 7.36−7.46 (m, 5 H), 7.51−7.56 (m, 2 H), 7.66 (d, J = 2.3 Hz, 1 H), 7.75 (s, 1 H), 8.07 (d, J = 8.8 Hz, 1 H), 12.43 (s, 1 H). MS (electrospray): 342 $(M - H)^-$.

2-(1-(Benzyloxycarbonyl)-5-chloro-1*H*-indol-3-yl)acetic acid was converted to benzyl 5-chloro-3-(3-chloro-2-oxopropyl)-1*H*-indole-1-carboxylate using general procedure IV, method A, with ethyl acetate used as the extraction solvent in the workup and the product purified by flash chromatography over silica gel (10−50% ethyl acetate in hexanes), resulting in a pale yellow solid, 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (d, J = 1.0 Hz, 2 H), 4.15 (s, 2 H), 5.44 (s, 2 H), 7.30 (dd, J = 8.8, 2.0 Hz, 1 H), 7.38−7.50 (m, 6 H), 7.65 (s, 1 H), 8.11 (br s, 1 H). MS (electrospray): 374 $(M - H)^-$.

Benzyl 5-chloro-3-(3-chloro-2-oxopropyl)-1*H*-indole-1-carboxylate was converted to compound **87** using general procedure V, and the product was purified by flash chromatography over silica gel (8−60% ethyl acetate in hexanes), resulting in a viscous orange oil, 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.78 (s, 2 H), 4.74 (s, 2 H), 5.44 (s, 2 H), 7.30 (d, J = 8.6 Hz, 1 H), 7.35−7.51 (m, 6 H), 7.64 (s, 1 H), 8.10 (s, 1 H). MS (electrospray): 398 $(M - H)^-$.

Benzyl 3-(3-Acetoxy-2-oxopropyl)-5-bromo-1*H*-indole-1-carboxylate (89): 2-(1-(Benzyloxycarbonyl)-5-bromo-1*H*-indol-3-yl)-acetic acid was prepared using general procedure III, purified by flash chromatography over silica gel (1−10% methanol in dichlo-

romethane with 0.5% triethylamine), and then converted back to the free acid by taking up the purified triethylammonium salt in 20% acetonitrile in water, acidifying to pH 1 with concentrated hydrochloric acid, and collecting the precipitate, a white powder, 53%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 2 H), 5.47 (s, 2 H), 7.38−7.46 (m, 3 H), 7.48−7.55 (m, 3 H), 7.73 (s, 1 H), 7.80 (d, J = 1.8 Hz, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 12.46 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{18}H_{15}BrNO_4$ (MH^+), 388.0179; found, 388.0172.

2-(1-(Benzyloxycarbonyl)-5-bromo-1*H*-indol-3-yl)acetic acid was converted to benzyl 5-bromo-3-(3-chloro-2-oxopropyl)-1*H*-indole-1-carboxylate using general procedure IV, method A, 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (d, J = 1.0 Hz, 2 H), 4.15 (s, 2 H), 5.44 (s, 2 H), 7.38−7.49 (m, 6 H), 7.58 (d, J = 1.8 Hz, 1 H), 7.63 (s, 1 H), 8.06 (br s, 1 H).

Benzyl 5-bromo-3-(3-chloro-2-oxopropyl)-1*H*-indole-1-carboxylate was converted to **89** using general procedure V and purified by flash chromatography over silica gel (24−34% ethyl acetate in hexanes), 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 3.77 (d, J = 1.0 Hz, 2 H), 4.74 (s, 2 H), 5.43 (s, 2 H), 7.36−7.49 (m, 6 H), 7.58 (dd, J = 2.0, 0.5 Hz, 1 H), 7.62 (s, 1 H), 8.06 (br s, 1 H).

Benzyl 3-(3-Acetoxy-2-oxopropyl)-5-methyl-1*H*-indole-1-carboxylate (91): 2-(1-(Benzyloxycarbonyl)-5-methyl-1*H*-indol-3-yl)-acetic acid was prepared using general procedure III, resulting in a lavender solid, 100%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3 H), 3.68 (d, J = 0.8 Hz, 2 H), 5.45 (s, 2 H), 7.16 (dd, J = 8.5, 1.6 Hz, 1 H), 7.34−7.46 (m, 4 H), 7.53 (dt, J = 6.4, 1.6 Hz, 2 H), 7.62 (s, 1 H), 7.95 (d, J = 8.3 Hz, 1 H), 12.39 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_4$ (MH^+), 324.1231; found, 324.1231. 2-(1-(Benzyloxycarbonyl)-5-methyl-1*H*-indol-3-yl)acetic acid was converted to benzyl 3-(3-chloro-2-oxopropyl)-5-methyl-1*H*-indole-1-carboxylate using general procedure IV, method A. The precipitate that accumulated upon bubbling of hydrogen chloride gas was collected, and the filtrate was then extracted with ether, resulting in a combined yield of 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3 H), 3.94 (d, J = 1.0 Hz, 2 H), 4.15 (s, 2 H), 5.44 (s, 2 H), 7.17 (d, J = 9.4 Hz, 1 H), 7.23 (dt, J = 1.5, 0.8 Hz, 1 H), 7.36−7.45 (m, 3 H), 7.46−7.50 (m, 2 H), 7.59 (s, 1 H), 8.04 (br s, 1 H). MS (electrospray): 402 $(M + H + CH_2O_2)^+$.

Benzyl 3-(3-chloro-2-oxopropyl)-5-methyl-1*H*-indole-1-carboxylate was converted to **91** using general procedure V and purified by flash chromatography over silica gel (15−35% ethyl acetate in hexanes), resulting in a peach-colored solid, 37%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3 H), 2.44 (s, 3 H), 3.78 (s, 2 H), 4.73 (s, 2 H), 5.43 (s, 2 H), 7.16 (d, J = 8.6 Hz, 1 H), 7.22−7.26 (m, 1 H), 7.34−7.44 (m, 3 H), 7.45−7.50 (m, 2 H), 7.57 (s, 1 H), 8.04 (s, 1 H). MS (electrospray): 426 $(M + H + CH_2O_2)^+$.

Benzyl 3-(3-Acetoxy-2-oxopropyl)-5-methoxy-1*H*-indole-1-carboxylate (93): 2-(1-(Benzyloxycarbonyl)-5-methoxy-1*H*-indol-3-yl)acetic acid was prepared using general procedure III, resulting in an off-white solid, 94%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 2 H), 3.78 (s, 3 H), 5.45 (s, 2 H), 6.95 (dd, J = 9.0, 1.6 Hz, 1 H), 7.09 (s, 1 H), 7.36−7.47 (m, 3 H), 7.50−7.55 (m, 2 H), 7.64 (s, 1 H), 7.95 (d, J = 8.6 Hz, 1 H), 12.41 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_5$ (MH^+), 340.1180; found, 340.1177.

2-(1-(Benzyloxycarbonyl)-5-methoxy-1*H*-indol-3-yl)acetic acid was converted to benzyl 3-(3-chloro-2-oxopropyl)-5-methoxy-1*H*-indole-1-carboxylate using general procedure IV, method A. When hydrogen chloride gas was bubbled through the ethereal diazoketone mixture, a significant amount of solid precipitated out of solution. This precipitate was collected and found to contain pure product. The filtrate was then worked up as described above, except that ethyl acetate was used as the extraction solvent instead of ether. The combined yield was 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3 H), 3.93 (d, J = 0.8 Hz, 2 H), 4.15 (s, 2 H), 5.43 (s, 2 H), 6.90 (d, J = 2.5 Hz, 1 H), 6.95 (dd, J = 9.1, 2.3 Hz, 1 H), 7.36−7.45 (m, 3 H), 7.45−7.50 (m, 2 H), 7.60 (s, 1 H), 8.06 (br s, 1 H). MS (electrospray): 372 $(M + H)^+$.

Benzyl 3-(3-chloro-2-oxopropyl)-5-methoxy-1*H*-indole-1-carboxylate was converted to **93** using general procedure V and recrystallized from ethanol, resulting in a pale mustard-yellow powder with small brown lumps, 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3 H), 3.77 (s, 2 H), 3.85 (s, 3 H), 4.73 (s, 2 H), 5.43 (s, 2 H), 6.89 (s, 1 H), 6.95 (d, J = 8.8 Hz, 1 H), 7.34−7.45 (m, 3 H), 7.45−7.50 (m, 2 H), 7.58 (s, 1 H), 8.06 (s, 1 H). MS (electrospray): 396 $(M + H)^+$.

Benzyl 3-(3-Acetoxy-2-oxopropyl)-2-methyl-1*H*-indole-1-carboxylate (95): 2-(1-(Benzyloxycarbonyl)-2-methyl-1*H*-indol-3-yl)-acetic acid was prepared using general procedure III, resulting in a pale pink solid, 98%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3 H), 3.65 (s, 2 H), 5.48 (s, 2 H), 7.19−7.25 (m, 2 H), 7.37−7.50 (m, 4 H), 7.53−7.57 (m, 2 H), 8.00−8.03 (m, 1 H), 12.34 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_4$ (MH^+), 324.1231; found, 324.1229.

2-(1-(Benzyloxycarbonyl)-2-methyl-1*H*-indol-3-yl)acetic acid was converted to benzyl 3-(3-chloro-2-oxopropyl)-2-methyl-1*H*-indole-1-carboxylate using general procedure IV, method A, 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 (s, 3 H), 3.91 (s, 2 H), 4.07 (s, 2 H), 5.48 (s, 2 H), 7.20−7.29 (m, 2 H), 7.34−7.46 (m, 4 H), 7.50 (d, 2 H), 8.10 (br s, 1 H). MS (electrospray): 356 $(M + H)^+$.

Benzyl 3-(3-chloro-2-oxopropyl)-2-methyl-1*H*-indole-1-carboxylate was converted to compound **95** using general procedure V and recrystallized from ethanol, resulting in an ivory powder, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3 H), 2.56 (s, 3 H), 3.77 (s, 2 H), 4.65 (s, 2 H), 5.47 (s, 2 H), 7.21−7.28 (m, 2 H), 7.34−7.45 (m, 4 H), 7.49 (dt, 1 H), 8.08−8.13 (m, 1 H). MS (electrospray): 380 $(M + H)^+$.

3-Hydroxyquinoline-4-carboxylic Acids. General Procedures VI. Method 1: The procedure described by Cragoe et al.[31] was followed. In a 50 mL two-necked round-bottomed flask fitted with a reflux condenser, the appropriate indoline-2,3-dione (3.5 mmol) was suspended in 4 mL of 6 M aqueous potassium hydroxide and heated to 100 °C. A solution of the acetoxymethyl ketone (4.41 mmol) in 4 mL of warm ethanol was then added by syringe in small portions over the course of 1 h. After the addition had been completed, the reaction mixture was refluxed for 4 additional hours. It was then cooled to room temperature, and ethanol was removed under reduced pressure. The residue was diluted with 20 mL of water, chilled for $^1/_2$ h, and filtered, and the filtrate was acidified to pH 1 with 1 M aqueous hydrochloric acid. The precipitate of crude acid was collected by filtration, washed with water, and dried under vacuum. **Method 2:** In a three-necked 250 mL round-bottomed flask fitted with a reflux condenser, under a nitrogen atmosphere, the indoline-2,3-dione (19.1 mmol) was taken up in 5 mL of ethanol and 17 mL of 10 M aqueous sodium hydroxide solution. The flask and contents were heated to reflux in an oil bath, with stirring. A solution of the acetoxymethyl ketone (24.8 mmol) in 32 mL of warm ethanol was then added in small portions via syringe over 1 h, and the solution was refluxed for an additional hour. After cooling to room temperature, the mixture was acidified with glacial acetic acid. If a precipitate was obtained, this was collected by filtration, washed with water, and dried under vacuum overnight. Otherwise, the crude product was extracted into ethyl acetate (2−3×), and the organic extracts were washed with brine (3×), dried over anhydrous magnesium sulfate, filtered, and evaporated. The crude acid was usually purified by (A) flash chromatography over silica gel, eluting with a 70 ethyl acetate/5 acetonitrile/2.5 methanol/2.5 water system to which 0.5% triethylamine had been added; the pure triethylammonium salt was then taken up in 20% acetonitrile in water and acidified with concentrated hydrochloric acid to precipitate the free acid; or (B) preparative HPLC (water/acetonitrile with 0.1% triethylamine) and converted back to free acid as described above. For either purification method, if the purified product precipitated out of solution upon acidification, it was collected by suction filtration, washed with water, and dried under vacuum overnight. Otherwise, it was extracted into ethyl acetate, and the organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated, and lyophilized.

2-(4-Chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (24): Reaction of isatin **10** with acetate **65**, using general procedure VI, method 2, gave a crude mixture

that was purified by method B, 16%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51−2.56 (m, 2 H), 3.37−3.42 (m, 2 H), 4.23 (s, 2 H), 4.33 (br s, 2 H), 7.18 (d, J = 9.1 Hz, 1 H), 7.27−7.33 (m, 2 H), 7.33−7.39 (m, 2 H), 8.95 (br s, 2 H), 9.31 (d, J = 9.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{20}H_{17}ClN_2O_3$ (MH^+), 369.10005; found, 369.101. HPLC (method 1, 97%; method 2, 98%).

2-((1*H*-Indol-3-yl)methyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (27): General procedure VI, method 2, was used, and purification was done by trituration with boiling ethanol, resulting in a yellow powder, 49%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.65−1.93 (m, 4 H), 2.83 (br s, 2 H), 3.24 (br s, 2 H), 4.41 (s, 2 H), 6.90−7.08 (m, 2 H), 7.13−7.36 (m, 3 H), 7.75 (d, J = 7.1 Hz, 1 H), 8.19 (s, 1 H), 10.84 (s, 1 H). Anal. ($C_{23}H_{20}N_2O_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{23}H_{21}N_2O_3$ (MH^+), 373.1547; found, 373.1548.

2-(4-Chloro-benzyl)-3-hydroxy-7,8,9,10-tetrahydro-benzo[*h*]-quinoline-4-carboxylic Acid (31): General procedure VI, method 1, was used, and purification was done by method A, resulting in canary yellow crystals, 41%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82 (m, 4 H), 2.83 (t, J = 5.6 Hz, 2 H), 3.16 (t, J = 5.7 Hz, 2 H), 4.31 (s, 2 H), 7.29 (d, J = 8.8 Hz, 1 H), 7.34 (s, 4 H), 8.18 (d, J = 8.8 Hz, 1 H). Anal. ($C_{21}H_{18}ClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{21}H_{18}ClNO_3$ (MH^+), 368.1048; found, 368.104.

3-Hydroxy-2-phenyl-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (49): General procedure VI, method 2, was used, resulting in a yellow powder, 20%, which was purified by method B. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76−1.93 (m, 4 H), 2.86 (t, J = 5.7 Hz, 2 H), 3.25 (t, J = 5.8 Hz, 2 H), 7.33 (d, J = 9.1 Hz, 1 H), 7.44−7.56 (m, 3 H), 8.09 (dd, J = 8.1, 1.52 Hz, 2 H), 8.28 (d, J = 8.8 Hz, 1 H). Anal. ($C_{20}H_{17}NO_3 \cdot 0.25H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{20}H_{17}NO_3$ (MH^+), 320.12812; found, 320.12807.

3-Hydroxy-2-phenylquinoline-4-carboxylic Acid (51): General procedure VI, method 2, was used, and the product was purified by trituration with boiling ethanol, resulting in a yellow powder, 19%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47−7.64 (m, 6 H), 7.99 (dd, J = 8.1, 1.01 Hz, 1 H), 8.03−8.08 (m, 2 H). Anal. ($C_{16}H_{11}NO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{16}H_{11}NO_3$ (MH^+), 266.08117; found, 266.08107.

Triethylammonium 3-Hydroxy-7,8-dimethyl-2-phenylquinoline-4-carboxylic Acid (53): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a tan foam, 72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, J = 7.20 Hz, 9 H), 2.39 (s, 3 H), 2.68 (s, 3 H), 3.09 (q, J = 7.3 Hz, 6 H), 7.25 (d, J = 8.8 Hz, 1 H), 7.32−7.59 (m, 3 H), 8.12−8.40 (m, 2 H), 9.21 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{18}H_{15}NO_3$ (MH^+), 294.1125; found, 294.1123. HPLC (method 1, 98.3%; method 2, 99%).

2-Benzyl-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (56): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 35%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72−1.92 (m, 4 H), 2.83 (t, J = 6.1 Hz, 2 H), 3.18 (t, J = 5.8 Hz, 2 H), 4.31 (s, 2 H), 7.14−7.21 (m, 1 H), 7.23−7.36 (m, 5 H), 8.24 (d, J = 7.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{19}NO_3$ (MH^+), 334.1438; found, 334.1438. HPLC (method 1, 96%; method 2, 98%).

3-Hydroxy-2-phenethyl-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (58): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 15%. ^{1}H NMR (500 MHz, D_2O): δ 1.77−1.90 (m, 4 H), 2.85 (t, J = 6.0 Hz, 3 H), 3.16 (t, J = 7.8 Hz, 2 H), 3.22 (t, J = 6.0 Hz, 2 H), 3.29 (t, J = 7.8 Hz, 2 H), 7.18 (t, J = 7.0 Hz, 1 H), 7.22−7.38 (m, 5 H), 8.24−8.32 (m, 1 H). Anal. ($C_{22}H_{21}NO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{22}H_{21}NO_3$ (MH^+), 348.15942; found, 348.15933.

3-Hydroxy-2-(4-(trifluoromethoxy)benzyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (60): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a canary yellow solid, 27%. ^{1}H NMR (400 MHz, DMF): δ 1.75−1.88 (m, 4 H), 2.83 (t, J = 5.3 Hz, 2 H), 3.15 (t, J = 5.6 Hz, 2 H), 4.34 (s, 2 H), 7.30−7.31 (m, 3 H), 7.44 (d, J = 8.6 Hz, 2 H), 8.21 (d, J = 9.1 Hz, 1 H). Anal. ($C_{22}H_{18}F_3NO_4 \cdot 0.1(C_2H_5)_3N$) C, H, N. HRMS (ESI$^+$) calcd for $C_{22}H_{18}F_3NO_4$ (MH^+), 418.1257; found, 418.1261.

2-(4-Carbamoylbenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (62): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 10%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73−1.91 (m, 4 H), 2.84 (t, J = 6.2 Hz, 2 H), 3.15 (t, J = 6.3 Hz, 2 H), 4.41 (s, 2 H), 7.29 (d, J = 9.1 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.83−7.91 (d, J = 8.9 Hz, 2 H), 8.49 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{20}N_2O_4$ (MH^+), 377.1496; found, 377.1497. HPLC (method 1, 95%; method 2, 98%).

2-(4-Carboxybenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-4-carboxylic Acid (63): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 15%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.68−1.96 (m, 4 H), 2.84 (t, J = 6.2 Hz, 2 H), 3.16 (t, J = 5.8 Hz, 2 H), 4.39 (s, 2 H), 7.30 (d, J = 8.8 Hz, 1 H), 7.42 (d, J = 8.6 Hz, 2 H), 7.69−7.82 (d, J = 8.6 Hz, 2 H), 8.43 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{19}NO_5$ (MH^+), 378.1336; found, 378.1343. HPLC (method 1, 95%; method 2, 99%).

2-(4-Cyanobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-4-carboxylic Acid (64): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.68−1.91 (m, 4 H), 2.83 (t, J = 5.3 Hz, 2 H), 3.13 (t, J = 5.7 Hz, 2 H), 4.40 (s, 2 H), 7.28 (d, J = 9.1 Hz, 1 H), 7.51 (d, J = 8.6 Hz, 2 H), 7.66−7.80 (d, J = 8.5 Hz, 2 H), 8.23 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{18}N_2O_3$ (MH^+), 359.1390; found, 359.1391. HPLC (method 1, 95%; method 2, 99%).

2-(3-Chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-4-carboxylic Acid (67): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a bright yellow powder, 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74−1.88 (m, 4 H), 2.83 (t, J = 4.3 Hz, 2 H), 3.15 (t, J = 4.6 Hz, 2 H), 4.32 (s, 2 H), 7.24−7.35 (m, 4 H), 7.39 (s, 1 H), 8.20 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{19}ClNO_3$ (MH^+), 368.1048; found, 368.1046. HPLC (method 1, 96%; method 2, 100%).

2-(2-Chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-4-carboxylic Acid (69): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a bright yellow powder, 24%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74 (br s, 4 H), 2.80 (br s, 2 H), 2.92 (br s, 2 H), 4.42 (s, 2 H), 7.22−7.32 (m, 4 H), 7.43−7.50 (m, 1 H), 8.23 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{19}ClNO_3$ (MH^+), 368.1048; found, 368.1047. HPLC (method 1, 100%; method 2, 100%).

2-(3,4-Dichlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (71): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a bright yellow powder, 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73−1.86 (m, 4 H), 2.81 (t, J = 6.1 Hz, 2 H), 3.12 (t, J = 5.9 Hz, 2 H), 4.30 (s, 2 H), 7.28 (t, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.1 Hz, 1 H), 7.59 (d, J = 2.0 Hz, 1 H), 8.19 (d, J = 8.6 Hz, 1 H). Anal. ($C_{21}H_{17}Cl_2NO_3 + 0.25H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{21}H_{18}Cl_2NO_3$ (MH^+), 402.0658; found, 402.0661.

3-Hydroxy-2-(thiophen-2-ylmethyl)-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (73): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a dark yellow powder, 4.8%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75−1.88 (m, 4 H), 2.83 (t, J = 5.7 Hz, 2 H), 3.17−3.25 (m, 2 H), 4.49 (s, 2 H), 6.89−6.94 (m, 1 H), 6.94−6.98 (m, 1 H), 7.27 (d, J = 9.1 Hz, 1 H), 7.32 (dd, J = 5.3, 1.3 Hz, 1 H), 8.18 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_3S$ (MH^+), 340.1002; found, 340.1011. HPLC (method 1, 100%; method 2, 100%).

3-Hydroxy-2-(thiophen-3-ylmethyl)-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (75): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a bright yellow powder, 22%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73−1.89 (m, 4 H), 2.83 (t, J = 4.9 Hz, 2 H), 3.18 (t, J = 5.7 Hz, 2 H), 4.32 (s, 2 H), 7.10 (d, J = 4.8 Hz, 1 H), 7.23

(s, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 7.40−7.47 (m, 1 H), 8.22 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_3S$ (MH^+), 340.1002; found, 340.1006. HPLC (method 1, 95%; method 2, 99%).

3-Hydroxy-2-(5-methylthiophen-2-yl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (77): General procedure VI, method 2, was used, and the product was purified by method B (twice), resulting in a fluffy light brown solid, 4.1%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78−1.92 (m, 4 H), 2.51 (s, 3 H), 2.83 (t, J = 5.2 Hz, 2 H), 3.23 (t, J = 5.7 Hz, 2 H), 6.90 (d, J = 2.8 Hz, 1 H), 7.25 (d, J = 8.8 Hz, 1 H), 8.00 (d, J = 3.5 Hz, 1 H), 8.30 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_3S$ (MH^+), 340.1002; found, 340.0997. HPLC (method 1, 97%; method 2, 98%).

2-(Benzo[*b*]thiophen-3-ylmethyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (79): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a bright yellow powder, 6.8%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71−1.85 (m, 4 H), 2.80 (t, J = 5.2 Hz, 2 H), 3.11 (t, J = 5.1 Hz, 2 H), 4.53 (s, 2 H), 7.25 (d, J = 8.8 Hz, 1 H), 7.30−7.45 (m, 3 H), 7.94 (d, J = 7.8 Hz, 1 H), 8.11 (d, J = 8.1 Hz, 1 H), 8.19 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{20}NO_3S$ (MH^+), 390.1159; found, 390.1167. HPLC (method 1, 97%; method 2, 100%).

2-(Benzofuran-3-ylmethyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (82): General procedure VI, method 2, was used, and the product was purified by method B (twice), resulting in a bright yellow powder, 2.7%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (s, 4 H), 2.82 (s, 2 H), 3.13 (s, 2 H), 4.38 (s, 2 H), 7.18−7.33 (m, 3 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.72 (d, J = 7.6 Hz, 1 H), 7.89 (s, 1 H), 8.22 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{20}NO_4$ (MH^+), 374.1387; found, 374.1385. HPLC (method 1, 98%; method 2, 99%).

3-Hydroxy-2-(3-methylbenzo[*b*]thiophen-2-ylmethyl)-7,8,9,-10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (84): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a fluffy light yellow solid, 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76−1.88 (m, 4 H), 2.50 (s, 3 H), 2.80 (t, J = 5.3 Hz, 2 H), 3.20 (t, J = 5.8 Hz, 2 H), 4.52 (s, 2 H), 7.16 (d, J = 8.8 Hz, 1 H), 7.25 (t, J = 7.6 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 8.1 Hz, 1 H), 8.68 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{24}H_{22}NO_3S$ (MH^+), 404.1315; found, 404.1312. HPLC (method 1, 100%; method 2, 100%).

Triethylammonium 2-(5-Chlorobenzo[*b*]thiophen-3-ylmethyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylate (86): General procedure VI, method 2, was used, and the product was purified by method B. The purified triethylammonium salt (6:5 acid/base stoichiometry) was too insoluble in aqueous acetonitrile to be converted back to the free acid by the usual method and was thus assayed in its salt form, resulting in a sunflower-yellow powder, 21%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, J = 7.2 Hz, 7.5 H), 1.72−1.87 (m, 4 H), 2.77 (t, J = 5.9 Hz, 2 H), 3.10 (dq, 5 H), 3.18 (t, J = 5.7 Hz, 2 H), 4.46 (s, 2 H), 7.08 (d, J = 8.8 Hz, 1 H), 7.35 (dd, J = 8.7, 2.2 Hz, 1 H), 7.59 (s, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 8.41 (d, J = 2.1 Hz, 1 H), 8.94 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{19}ClNO_3S$ (MH^+), 424.0769; found, 424.0770. HPLC (method 1, 100%; method 2, 100%).

2-((5-Chloro-1*H*-indol-3-yl)methyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (88): General procedure VI, method 2, was used, and the product was purified by trituration with boiling ethanol, resulting in a mustard-yellow powder, 36%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77−1.91 (m, 4 H), 2.83 (t, J = 6.1 Hz, 2 H), 3.28 (t, J = 5.9 Hz, 2 H), 4.38 (s, 2 H), 7.02 (dd, J = 8.6, 2.0 Hz, 1 H), 7.22−7.33 (m, 3 H), 7.91 (d, J = 2.0 Hz, 1 H), 8.19 (d, J = 8.8 Hz, 1 H), 11.04 (s, 1 H). Anal. ($C_{23}H_{19}ClN_2O_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{23}H_{20}ClN_2O_3$ (MH^+), 407.1157; found, 407.1158.

2-((5-Bromo-1*H*-indol-3-yl)methyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (90): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a bright yellow powder, 8.9%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77−1.93 (m, 4 H), 2.84 (t, J = 5.7 Hz, 2 H), 3.30 (t, J = 6.1 Hz, 2 H), 4.38 (s, 2 H), 7.12 (dd, J = 8.5, 1.9 Hz, 1 H), 7.23−7.30 (m, 3 H), 8.09 (d, J = 1.8 Hz, 1 H), 8.17 (d, J = 8.3 Hz, 1 H), 11.06 (s, 1 H). Anal. ($C_{23}H_{19}BrN_2O_3$ + 0.5H_2O) C, H, N. HRMS (ESI$^+$) calcd for $C_{23}H_{20}BrN_2O_3$ (MH^+), 451.0652; found, 451.0659.

3-Hydroxy-2-((5-methyl-1*H*-indol-3-yl)methyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (92): General procedure VI, method 2, was used, and the product was purified by trituration with boiling ethanol, resulting in a bright yellow powder, 36%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76−1.92 (m, 4 H), 2.36 (s, 3 H), 2.83 (s, 2 H), 3.29 (s, 2 H), 4.37 (s, 2 H), 6.85 (d, J = 7.8 Hz, 1 H), 7.12 (d, J = 1.3 Hz, 1 H), 7.18 (d, J = 8.1 Hz, 1 H), 7.24 (d, J = 8.8 Hz, 1 H), 7.65 (s, 1 H), 8.20 (d, J = 7.6 Hz, 1 H), 10.68 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{24}H_{23}N_2O_3$ (MH^+), 387.1703; found, 387.1702. HPLC (method 1, 100%; method 2, 100%).

3-Hydroxy-2-((5-methoxy-1*H*-indol-3-yl)methyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (94): General procedure VI, method 2, was used, and the product was purified by trituration with boiling ethanol, resulting in a bright yellow powder, 33%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76−1.89 (m, 4 H), 2.83 (t, J = 5.7 Hz, 2 H), 3.28 (t, J = 5.6 Hz, 2 H), 3.73 (s, 3 H), 4.37 (s, 2 H), 6.66 (dd, J = 8.7, 2.4 Hz, 1 H), 7.16 (d, J = 2.3 Hz, 1 H), 7.18 (d, J = 8.8 Hz, 1 H), 7.24 (d, J = 5.3 Hz, 1 H), 7.26 (s, 1 H), 8.21 (d, J = 6.8 Hz, 1 H), 10.68 (s, 1 H). Anal. ($C_{24}H_{22}N_2O_4$ + 0.5C_2H_5OH) C, H, N. HRMS (ESI$^+$) calcd for $C_{24}H_{23}N_2O_4$ (MH^+), 403.1653; found, 403.1649.

3-Hydroxy-2-((2-methyl-1*H*-indol-3-yl)methyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (96): General procedure VI, method 2, was used, and the product was purified by trituration with boiling ethanol, resulting in a bright yellow powder, 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77−1.91 (m, 4 H), 2.51 (s, 3 H), 2.83 (t, J = 5.9 Hz, 2 H), 3.27 (t, J = 5.9 Hz, 2 H), 4.33 (s, 2 H), 6.85 (td, J = 7.3, 1.3 Hz, 1 H), 6.91 (td, J = 7.5, 1.3 Hz, 1 H), 7.17 (d, J = 7.8 Hz, 1 H), 7.23 (d, J = 8.8 Hz, 1 H), 7.71 (d, J = 7.6 Hz, 1 H), 8.23 (d, J = 8.8 Hz, 1 H), 10.73 (s, 1 H). Anal. ($C_{24}H_{22}N_2O_3$ + 0.5C_2H_5OH) C, H, N. HRMS (ESI$^+$) calcd for $C_{24}H_{23}N_2O_3$ (MH^+), 387.1703; found, 387.1703.

2-(4-Chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (123): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 42%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.36 (s, 2 H), 7.26−7.42 (m, 5 H), 7.51−7.68 (m, 2 H), 7.88−8.02 (m, 1 H), 8.78 (br s, 1 H). HRMS (ESI$^+$) calcd for $C_{17}H_{12}ClNO_3$ (MH^-), 312.04330; found, 312.0437. HPLC (method 1, 95%; method 2, 95%).

2-(4-Chlorobenzyl)-3-hydroxy-8-methylquinoline-4-carboxylic Acid (125): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a bright yellow powder, 38%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (s, 3 H), 4.33 (s, 2 H), 7.35 (m, 4 H), 7.44 (m, 2 H), 8.30 (dd, J = 8.1, 1.3 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{18}H_{15}ClNO_3$ (MH^+), 328.0735; found, 328.0736. HPLC (method 1, 100%; method 2, 100%).

2-(4-Chlorobenzyl)-8-ethyl-3-hydroxyquinoline-4-carboxylic Acid (127): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a bright yellow powder, 25%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, J = 7.5 Hz, 3 H), 3.11 (q, J = 7.3 Hz, 2 H), 4.32 (s, 2 H), 7.34 (s, 4 H), 7.40 (d, J = 7.1 Hz, 1 H), 7.46 (t, 1 H), 8.32 (d, J = 8.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{17}ClNO_3$ (MH^+), 342.0892; found, 342.0890. HPLC (method 1, 100%; method 2, 100%).

2-(4-Chlorobenzyl)-3-hydroxy-8-isopropylquinoline-4-carboxylic Acid (129): General procedure VI, method 1, was used, and the product was purified by method A and then recrystallized from acetonitrile, resulting in a yellow powder, 13%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (d, J = 7.1 Hz, 6 H), 4.11 (septet, 1 H), 4.33 (s, 2 H), 7.34 (s, 4 H), 7.43 (dd, J = 7.3, 1.0 Hz, 1 H), 7.51 (m, 1 H), 8.26 (dd, J = 8.5, 1.4 Hz, 1 H). Anal. ($C_{20}H_{18}ClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{20}H_{19}ClNO_3$ (MH^+), 356.1048; found, 356.1048.

8-(*sec*-Butyl)-2-(4-chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (131): General procedure VI, method 1, was used, and the product was purified by method A and then method B, resulting in a fluffy bright yellow solid, 3.9%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.74 (t, J = 7.3 Hz, 3 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.61 (m, 2 H), 3.91 (m, 1 H), 4.32 (dd, 2 H), 7.34 (m, 4 H), 7.39 (d, J = 6.1 Hz, 1 H), 7.51 (dd, J = 8.6, 7.3 Hz, 1 H), 8.25 (dd, J = 8.3, 1.3 Hz, 1 H). Anal. ($C_{21}H_{20}ClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{21}H_{21}ClNO_3$ (MH$^+$), 370.1205; found, 370.1204.

8-*tert*-Butyl-2-(4-chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (133): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 10%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 9 H), 4.34 (s, 2 H), 7.29−7.38 (m, 4 H), 7.44 (d, J = 5.1 Hz, 2 H), 8.17 (t, J = 4.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{20}ClNO_3$ (MH$^+$), 370.1204; found, 370.1205. HPLC (method 1, 97%; method 2, 99%).

2-(4-Chlorobenzyl)-3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic Acid (134): General procedure VI, method 1, was used, and the product was purified by method A, resulting in an off-white powder, 42%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.32 (s, 2 H), 7.34 (m, 4 H), 7.68 (t, 1 H), 7.94 (d, J = 7.3 Hz, 1 H), 8.83 (d, J = 8.6 Hz, 1 H). Anal. ($C_{18}H_{11}ClF_3NO_3$): C, H, N. HRMS (ESI$^+$) calcd for $C_{18}H_{12}ClF_3NO_3$ (MH$^+$), 382.0453; found, 382.0449.

2-(4-Chlorobenzyl)-3-hydroxy-8-(trifluoromethoxy)quinoline-4-carboxylic Acid (136): General procedure VI, method 1, was used, and the product was purified by method A, resulting in an ivory powder, 16%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.33 (s, 2 H), 7.33 (m, 4 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.61 (t, 1 H), 8.57 (dd, J = 8.5, 1.4 Hz, 1 H). Anal. ($C_{18}H_{11}ClF_3NO_4$) C, H, N. HRMS (ESI$^+$) calcd for $C_{18}H_{12}ClF_3NO_4$, 398.0402; found, 398.0401.

2-(4-Chlorobenzyl)-3-hydroxy-8-phenylquinoline-4-carboxylic Acid (138): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a fluffy bright yellow solid, 11%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.23 (s, 2 H), 7.27 (m, 2 H), 7.32 (m, 2 H), 7.37 (m, 3 H), 7.52 (m, 2 H), 7.56 (dd, J = 7.3, 1.5 Hz, 1 H), 7.63 (m, 1 H), 8.46 (dd, J = 8.3, 1.5 Hz, 1 H). Anal. ($C_{23}H_{16}ClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{23}H_{17}ClNO_3$ (MH$^+$), 390.0892; found, 390.0890.

2-(4-Chlorobenzyl)-3-hydroxy-8-(thien-3-yl)quinoline-4-carboxylic Acid (140): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a bright yellow powder, 37%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.34 (s, 2 H), 7.36 (dd, 4 H), 7.47 (dd, J = 5.1, 3.0 Hz, 1 H), 7.54 (m, 1 H), 7.58 (m, 1 H), 7.79 (m, 2 H), 8.36 (dd, J = 8.5, 1.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{15}ClNO_3S$ (MH$^+$), 396.0456; found, 396.0459. HPLC (method 1, 100%; method 2, 100%).

2-(4-Chlorobenzyl)-8-(fur-3-yl)-3-hydroxyquinoline-4-carboxylic Acid (142): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a mustard-yellow powder, 15%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (s, 2 H), 7.09 (d, J = 1.8 Hz, 1 H), 7.39 (q, J = 8.6 Hz, 4 H), 7.56 (dd, J = 8.46, 7.5 Hz, 1 H), 7.67 (t, J = 1.8 Hz, 1 H), 7.84 (dd, J = 7.3, 1.3 Hz, 1 H), 8.07 (s, 1 H), 8.30 (dd, J = 8.6, 1.0 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{15}ClNO_4$ (MH$^+$), 380.0684; found, 380.0689. HPLC (method 1, 100%; method 2, 100%).

8-Bromo-2-(4-chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (144): General procedure VI, method 1, was used, and the product was purified by method A and then recrystallized from acetonitrile, resulting in a large bright yellow crystals, 23%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.35 (s, 2 H), 7.35 (m, 4 H), 7.46 (dd, J = 8.6, 7.6 Hz, 1 H), 7.92 (dd, J = 7.5, 1.1 Hz, 1 H), 8.50 (dd, J = 8.6, 1.3 Hz, 1 H). Anal. ($C_{17}H_{11}BrClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{12}BrClNO_3$ (MH$^+$), 391.9684; found, 391.9689.

8-Chloro-2-(4-chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (146): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow powder, 15%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.34 (s, 2 H), 7.34 (s, 4 H), 7.51 (dd, J = 8.6, 7.6 Hz, 1 H), 7.71 (dd, J = 7.5, 1.1 Hz, 1 H), 8.54 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{17}H_{11}Cl_2NO_3$ (MH$^+$), 348.01888; found, 348.01889. HPLC (method 1, 96%; method 2, 100%).

2-(4-Chlorobenzyl)-8-fluoro-3-hydroxyquinoline-4-carboxylic Acid (148): General procedure VI, method 1, was used, and the product was purified by method A and then recrystallized from ethanol/benzene, resulting in an off-white powder, 10%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.34 (s, 2 H), 7.37 (m, 5 H), 7.55 (m, 1 H), 8.34 (d, J = 8.6 Hz, 1 H). Anal. ($C_{17}H_{11}ClFNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{12}ClFNO_3$ (MH$^+$), 332.0484; found, 332.0481.

2-(4-Chlorobenzyl)-3-hydroxyquinoline-4,8-dicarboxylic Acid (150): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow powder, 10%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.42 (s, 2 H), 7.28−7.46 (m, 4 H), 7.69 (dd, J = 8.6, 7.3 Hz, 1 H), 8.23 (dd, J = 7.2, 1.1 Hz, 1 H), 9.06 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{18}H_{12}ClNO_5$ (MH$^+$), 358.0477; found, 358.0476. HPLC (method 1, 96%; method 2, 98%).

8-(4-Chlorobenzyl)-7-hydroxy-2,3-dihydro-1*H*-9-aza-cyclopenta-[*a*]naphthalene-6-carboxylic Acid (152): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a bright yellow powder, 14%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (quint, 2 H), 3.05 (t, J = 7.3 Hz, 2 H), 3.28 (t, J = 7.5 Hz, 2 H), 4.32 (s, 2 H), 7.33 (s, 4 H), 7.49 (d, J = 8.3 Hz, 1 H), 8.36 (d, J = 8.1 Hz, 1 H). Anal. ($C_{20}H_{16}ClNO_3 + 0.5H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{20}H_{17}ClNO_3$ (MH$^+$), 354.0892; found, 354.0898.

2-(4-Chlorobenzyl)-3-hydroxy-7-methylquinoline-4-carboxylic Acid (154): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow powder, 36%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99 (s, 3 H), 4.34 (s, 2 H), 7.30−7.39 (m, 4 H), 7.45 (dd, J = 8.8, 1.5 Hz, 1 H), 7.74 (s, 1 H), 8.60−8.85 (br s, 1 H). HRMS (ESI$^+$) calcd for $C_{18}H_{14}ClNO_3$ (MH$^+$), 328.0735; found, 328.0736. HPLC (method 1, 97%; method 2, 98%).

2-(4-Chlorobenzyl)-7-ethyl-3-hydroxyquinoline-4-carboxylic Acid (156): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow powder, 40%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27 (t, J = 7.6 Hz, 3 H), 2.78 (q, J = 7.6 Hz, 2 H), 4.35 (s, 2 H), 7.23−7.41 (m, 4 H), 7.51 (dd, J = 8.8, 1.8 Hz, 1 H), 7.75 (d, J = 1.3 Hz, 1 H), 8.74 (br s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{16}ClNO_3$ (MH$^+$), 342.0891; found, 342.0892. HPLC (method 1, 96%; method 2, 99%).

7-Chloro-2-(4-chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (158): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow powder, 32%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.31 (s, 2 H), 7.33 (s, 4 H), 7.60 (dd, J = 9.2, 2.4 Hz, 1 H), 7.94 (d, J = 2.3 Hz, 1 H), 8.73 (d, J = 9.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{17}H_{11}Cl_2NO_3$ (MH$^+$), 348.0189; found, 348.019. HPLC (method 1, 96%; method 2, 98%).

2-(4-Chlorobenzyl)-3-hydroxy-6-phenylquinoline-4-carboxylic Acid (160): General procedure VI, method 1, was used, and the product was purified by method A, resulting in a bright yellow powder, 14%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.35 (s, 2 H), 7.36 (s, 4 H), 7.43 (t, J = 7.3 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 2 H), 7.74 (d, J = 7.3 Hz, 2 H), 7.87 (dd, J = 8.5, 1.9 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 1 H), 9.10 (br s, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{17}ClNO_3$ (MH$^+$), 390.0892; found, 390.0894. HPLC (method 1, 100%; method 2, 100%).

2-(4-Chlorobenzyl)-3-hydroxy-5-methoxy-8-phenylquinoline-4-carboxylic Acid (161): General procedure VI, method 2, was used, and the product was purified by method B, resulting in an orange solid, 12%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3 H), 3.41 (s, 2 H), 6.76 (d, J = 8.3 Hz, 1 H), 7.07 (d, J = 8.3 Hz, 1 H), 7.13−7.41 (m, 9 H).

6-Bromo-2-(4-chlorobenzyl)-3-hydroxyquinoline-4-carboxylic Acid (163): General procedure VI, method 2, was used, and the product was purified by method B, resulting in a yellow solid, 24%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.29 (s, 2 H), 7.33 (s, 4 H), 7.62 (dd, J = 8.4, 2.3 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 9.07 (d, J = 2.3 Hz, 1 H). Anal. ($C_{17}H_{11}BrClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{11}BrClNO_3$ (MH$^+$), 391.9684; found, 391.9686.

2-((1*H*-Indol-3-yl)methyl)-8-ethyl-3-hydroxyquinoline-4-carboxylic Acid (166): Reaction of isatin **126** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 16%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, J = 7.5 Hz, 3 H), 3.20 (q, J = 7.5 Hz, 2 H), 4.42 (s, 2 H), 6.93 (t, J = 7.5 Hz, 1 H), 6.98−7.08 (m, 1 H), 7.19 (d, J = 2.3 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 1 H), 7.35−7.49 (m, 2 H), 7.75 (d, J = 7.8 Hz, 1 H), 8.31 (d, J = 9.1 Hz, 1 H), 10.84 (s, 1 H). Anal. ($C_{21}H_{18}N_2O_3 + 0.4H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{21}H_{18}N_2O_3$ (MH^+), 347.13902; found, 347.13896.

3-Hydroxy-2-(1*H*-indol-3-ylmethyl)-8-isopropylquinoline-4-carboxylic Acid (167): Reaction of isatin **128** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 13%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27 (d, J = 8.0 Hz, 6 H), 4.28−4.34 (m, 1 H), 4.32−4.37 (s, 2 H), 6.91 (m, 1 H), 7.01 (m, 1 H), 7.13−7.19 (m, 1 H), 7.18−7.38 (m, 3 H), 7.78 (d, J = 8.0 Hz, 1 H), 8.79−9.09 (m, 1 H), 8.85−8.95 (br s, 1 H) 10.66−10.84 (br s, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{20}N_2O_3$ (MH^+), 361.15467; found, 361.155. HPLC (method 1, 97%; method 2, 97%).

2-((1*H*-Indol-3-yl)methyl)-8-bromo-3-hydroxyquinoline-4-carboxylic Acid (168): Reaction of isatin **143** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 10%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (s, 2 H), 6.89−6.97 (m, 1 H), 6.97−7.06 (m, 1 H), 7.19−7.38 (m, 3 H), 7.78 (dd, J = 7.5, 1.1 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 1 H), 8.90 (d, J = 8.1 Hz, 1 H), 10.81 (br s, 1 H). Anal. ($C_{19}H_{13}BrN_2O_3 + 0.3H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{19}H_{13}BrN_2O_3$ (MH^+), 397.01823; found, 397.01836.

2-((1*H*-Indol-3-yl)methyl)-8-chloro-3-hydroxyquinoline-4-carboxylic Acid (169): Reaction of isatin **145** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 15%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.41 (s, 2 H), 6.85−6.98 (m, 1 H), 6.97−7.09 (m, 1 H), 7.22 (d, J = 2.3 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.35−7.49 (m, 1 H), 7.55−7.68 (m, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 8.76 (d, J = 9.1 Hz, 1 H), 10.83 (br s, 1 H). Anal. ($C_{19}H_{13}ClN_2O_3 + 0.7H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{19}H_{13}ClN_2O_3$ (MH^+), 353.06875; found, 353.06867.

2-((1*H*-Indol-3-yl)methyl)-8-fluoro-3-hydroxyquinoline-4-carboxylic Acid (170): Reaction of isatin **147** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 50%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.41 (s, 2 H), 6.88−6.98 (m, 1 H), 6.99−7.06 (m, 1 H), 7.16 (d, J = 2.3 Hz, 1 H), 7.28−7.35 (m, 2 H), 7.44−7.53 (m, 1 H), 7.71 (d, J = 7.8 Hz, 1 H), 8.42 (d, J = 8.8 Hz, 1 H), 10.85 (s, 1 H). Anal. ($C_{19}H_{13}FN_2O_3 + 0.3H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{19}H_{13}FN_2O_3$ (MH^+), 337.0983; found, 337.09835.

3-Hydroxy-2-(1*H*-indol-3-ylmethyl)-8-(3-thienyl)quinoline-4-carboxylic Acid (171): Reaction of isatin **139** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 31%. ^{1}H NMR (400 MHz, MeOD): δ 4.85 (s, 2 H), 7.31 (t, J = 8.0 Hz, 1 H), 7.45 (t, J = 8.0 Hz, 1 H), 7.54−7.60 (m, 1 H), 7.65−8.04 (m, 8 H), 9.58 (d, J = 8.0 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{16}N_2O_3S$ (MH^+), 401.09544; found, 401.0948. HPLC (method 1, 100%; method 2, 98%).

2-((1*H*-Indol-3-yl)methyl)-3-hydroxy-8-(trifluoromethoxy)-quinoline-4-carboxylic Acid (172): Reaction of isatin **135** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a yellow solid, 14%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.38 (s, 2 H), 6.91 (t, J = 7.5 Hz, 1 H), 6.95−7.09 (m, 1 H), 7.17 (d, J = 2.3 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.34−7.45 (m, 1 H), 7.45−7.58 (m, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 8.90 (d, J = 8.8 Hz, 1 H), 10.82 (s, 1 H). Anal. [$C_{20}H_{13}F_3N_2O_4 + 0.3(C_2H_5)_3N$] C, H, N. HRMS (ESI$^+$) calcd for $C_{20}H_{13}F_3N_2O_4$ (MH^+), 403.09002; found, 403.09004.

2-((1*H*-Indol-3-yl)methyl)-3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic Acid (173): Reaction of isatin **35** with acetate **80** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a brown powder, 12%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.43 (s, 2 H), 6.91 (td, J = 7.9, 1.0 Hz, 1 H), 7.01 (td, J = 7.5, 1.1 Hz, 1 H), 7.24 (d, J = 2.3 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.66 (t, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 7.95 (d, J = 7.6 Hz, 1 H), 8.77 (d, J = 8.6 Hz, 1 H), 10.87 (s, 1 H). Anal. ($C_{20}H_{13}F_3N_2O_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{20}H_{14}F_3N_2O_3$ (MH^+), 387.0951; found, 387.0949.

2-((5-Chloro-1*H*-indol-3-yl)methyl)-3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic Acid (174): Reaction of isatin **35** with acetate **87** using general procedure VI, method 2, gave a crude mixture that was purified by method B, resulting in a fluffy brown solid, 7.9%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (s, 2 H), 7.00 (d, J = 8.1 Hz, 1 H), 7.31 (d, J = 8.6 Hz, 1 H), 7.35 (s, 1 H), 7.67 (t, J = 8.1 Hz, 1 H), 7.78 (s, 1 H), 7.96 (d, J = 7.8 Hz, 1 H), 8.77 (d, J = 8.8 Hz, 1 H), 11.09 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{20}H_{13}ClF_3N_2O_3$ (MH^+), 421.0562; found, 421.0563. HPLC (method 1, 99%; method 2, 100%).

2-(3-Indolylmethylene)quinolinesalicylic Acid Library Synthesis. General Procedure VII. To a Genevac reaction carousel with heating and cooling capabilities was attached 10 Genevac reaction tubes with inert gas attachments. The reaction tubes were flushed with nitrogen gas and then added to each tube were the appropriate isatin (1.0 equiv), 5 mL of ethanol, and 0.6 mL of 10.0 N aqueous NaOH. These were heated to reflux and then a solution of benzyl 3-(3-acetoxy-2-oxopropyl)-1*H*-indole-1-carboxylate (**80**, 0.300 g, 0.82 mmol, 1.3 equiv.) in 3 mL of ethanol was added to each tube and allowed to stir at reflux for 12 h. Thereaction mixture was neutralized with 3 mL of glacial acetic acid and poured into a separatory funnel containing 75 mL of water. The reaction mixture was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with three 100 mL portions of water and 100 mL of brine. The solution was dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material was purified via reverse-phase HPLC (water/acetonitrile with 0.1% triethylamine); the product was isolated from the HPLC fraction by acidifying the solution with a few drops of concentrated HCl, followed by extraction into ethyl acetate and concentration in vacuo. The residue was then redissolved into 1 mL of acetonitrile, diluted with 15 mL of water, frozen, and lyophilized to give the desired product as a fine lyophilized powder.

2-((1*H*-Indol-3-yl)methyl)-3-hydroxyquinoline-4-carboxylic Acid (164): Reaction of isatin **48** with acetate **80** resulted in a yellow solid, 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.47 (s, 2 H), 6.96 (t, J = 7.5 Hz, 1 H), 7.05 (t, J = 7.6 Hz, 1 H), 7.21 (s, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.48−7.65 (m, 2 H), 7.71 (d, J = 7.6 Hz, 1 H), 7.96 (d, 1 H), 10.92 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{14}N_2O_3$ (MH^+), 319.1077; found, 319.1076. HPLC (method 1, 100%; method 2, 100%).

2-((1*H*-Indol-3-yl)methyl)-6-bromo-3-hydroxyquinoline-4-carboxylic Acid (181): yellow solid, 31%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.41 (s, 2 H), 6.95 (t, J = 7.5 Hz, 1 H), 7.04 (t, J = 7.3 Hz, 1 H), 7.17 (d, J = 2.1 Hz, 1 H), 7.31 (d, J = 7.8 Hz, 1 H), 7.63 (dd, J = 8.4, 2.02 Hz, 1 H), 7.68 (d, J = 7.6 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 9.13 (s, 1 H), 10.89 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{13}BrN_2O_3$ (MH^+), 397.0183; found, 397.0183. HPLC (method 1, 97%; method 2, 97%).

2-((1*H*-Indol-3-yl)methyl)-7-bromo-3-hydroxyquinoline-4-carboxylic Acid (178): yellow solid, 31%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.41 (s, 2 H), 6.91−6.98 (m, 1 H), 7.00−7.08 (m, 1 H), 7.17 (d, J = 2.3 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 1 H), 7.49−7.84 (m, 2 H), 8.09 (d, J = 2.0 Hz, 1 H), 8.73 (s, 1 H), 10.88 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{13}BrN_2O_3$ (MH^+), 397.0183; found, 397.0182. HPLC (method 1, 100%; method 2, 96%).

2-((1*H*-indol-3-yl)methyl)-3-hydroxy-6-(trifluoromethoxy)-quinoline-4-carboxylic Acid (185): yellow solid, 35%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.42 (s, 2 H), 6.90−6.98 (m, 1 H), 7.00−7.07 (m, 1 H), 7.17 (d, J = 2.5 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 1 H), 7.47 (d, J = 8.8 Hz, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 8.92 (s, 1 H), 10.88 (s, 1 H). HRMS (ESI$^+$)

calcd for $C_{20}H_{13}F_3N_2O_4$ (MH^+), 403.09; found, 403.0898. HPLC (method 1, 100%; method 2, 99%).

2-((1*H*-Indol-3-yl)methyl)-6-fluoro-3-hydroxyquinoline-4-carboxylic Acid (183): yellow solid, 34%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.41 (s, 2 H), 6.90−7.00 (m, 1 H), 7.00−7.09 (m, 1 H), 7.18 (d, J = 2.5 Hz, 1 H), 7.27−7.36 (m, 1 H), 7.36−7.47 (m, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.97 (dd, J = 9.2, 5.9 Hz, 1 H), 8.70 (s, 1 H), 10.89 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{19}H_{13}FN_2O_3$ (MH^+), 337.0983; found, 337.0981. HPLC (method 1, 100%; method 2, 97%).

2-((1*H*-Indol-3-yl)methyl)-3-hydroxy-6-methylquinoline-4-carboxylic Acid (180): yellow solid, 37%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3 H), 4.46 (s, 2 H), 6.91−7.00 (m, 1 H), 7.01−7.10 (m, 1 H), 7.20 (d, J = 1.8 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.42 (dd, J = 8.6, 1.77 Hz, 1 H), 7.70 (d, J = 7.6 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 1 H), 8.78 (s, 1 H), 10.93 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{20}H_{16}N_2O_3$ (MH^+), 333.1234; found, 333.1234. HPLC (method 1, 100%; method 2, 100%).

2-((1*H*-Indol-3-yl)methyl)-3-hydroxy-7-methylquinoline-4-carboxylic Acid (175): yellow solid, 17%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.97 (t, J = 7.5 Hz, 1 H), 7.05 (t, J = 7.5 Hz, 1 H), 7.20 (d, J = 1.0 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.46 (d, J = 7.8 Hz, 1 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.75 (s, 1 H), 8.94 (s, 1 H), 10.93 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{20}H_{16}N_2O_3$ (MH^+), 333.1234; found, 333.1233. HPLC (method 1, 100%; method 2, 100%).

2-((1*H*-Indol-3-yl)methyl)-3-hydroxy-8-methylquinoline-4-carboxylic Acid (165): Reaction of isatin **124** with acetate **80**, resulted in a yellow solid, 24%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.72 (s, 3 H), 4.43 (s, 2 H), 6.95 (t, J = 7.5 Hz, 1 H), 7.02 (t, J = 7.5 Hz, 1 H), 7.19 (s, 1 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.36−7.48 (m, 2 H), 7.77 (d, J = 7.8 Hz, 1 H), 8.30 (s, 1 H), 10.84 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{20}H_{16}N_2O_3$ (MH^+), 333.1234; found, 333.1233. HPLC (method 1, 98%; method 2, 99%).

3-Hydroxy-2-(1*H*-indol-3-yl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (97): In a 25 mL round-bottomed flask fitted with a reflux condenser, 6,7,8,9-tetrahydro-1*H*-benzo[*g*]-indole-2,3-dione (**54**; 250 mg, 1.25 mmol) was suspended in 1 mL of 10 M aqueous sodium hydroxide and heated to 100 °C. A solution of 2-hydroxy-1-(1*H*-indol-3-yl)ethanone (326 mg, 1.86 mmol) in 2 mL of warm ethanol was then added in small portions over the course of 1 h. After the addition had been completed, the reaction mixture was refluxed for four additional hours. It was then cooled to room temperature, and ethanol was removed under reduced pressure. The residue was diluted with 20 mL of water, chilled for $^1/_2$ h, and filtered, and the filtrate was acidified to pH 1 with 1 M aqueous hydrochloric acid. The precipitate of crude acid was collected by filtration, washed with water, and dried under vacuum. The crude mixture was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and converted back to free acid as described above to give a yellow solid (111 mg, 25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77−1.93 (m, 2 H), 1.91−2.04 (m, 2 H), 2.88 (t, J = 6.1 Hz, 2 H), 3.39 (t, J = 5.9 Hz 2 H), 7.20−7.28 (m, 3 H), 7.36−7.68 (m, 1 H), 8.40 (d, J = 8.1 Hz, 1 H), 8.59 (d, J = 2.8 Hz, 1 H), 8.93 (br s, 1 H), 11.64 (s, 1 H). Anal. ($C_{22}H_{18}N_2O_3$·0.4H_2O) C, H, N. HRMS (ESI$^+$) calcd for $C_{22}H_{18}N_2O_3$ (MH^+), 359.139; found, 359.1389.

***N*-Carbonyl Derivatives of 27. General Procedure VIII.** To a 10 mL microwave vial were added 2-[(1*H*-Indol-3-yl)methyl]-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic acid (**27**, 0.100 g, 0.269 mmol), anhydrous acetonitrile (3 mL), triethylamine (0.11 mL, 82 mg, 0.81 mmol), *N*,*N*-dimethylaminopyridine (33 mg, 0.27 mmol), and the desired acylating agent (3.23 mmol). The vial was crimp-sealed and heated in a microwave cavity for 10 min at 150 °C until the LC-MS analysis showed nearly complete conversion to the bisacylated product. The contents of the vial were then rinsed into a 25 mL round-bottomed flask with methanol and evaporated. The residue was taken up in 2.5 mL of methanol, 1 mL of tetrahydrofuran, 1 mL of water, and lithium hydroxide monohydrate (45 mg, 1.1 mmol) was added. This mixture was stirred overnight at room temperature until the LC-MS analysis showed that most of the bisacylated product had been converted to the monoacylated product. Aqueous hydrochloric acid (1 M) was then added until an acidic pH was reached, and the solution was evaporated. The crude product was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and then either converted back to the free acid as described above and lyophilized or lyophilized directly after concentration of the eluent solution to give the triethylammonium salt.

Triethylammonium 3-Hydroxy-2-((1-(2-phenylacetyl)-1*H*-indol-3-yl)methyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylate (98): fluffy beige solid, 14%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, J = 7.2 Hz, 9 H), 1.71−1.84 (m, 4 H), 2.76 (t, J = 5.6 Hz, 2 H), 2.88 (q, J = 6.7 Hz, 6 H), 3.12 (t, J = 5.4 Hz, 2 H), 4.32 (s, 2 H), 4.37 (s, 2 H), 7.04 (d, J = 8.8 Hz, 1 H), 7.19−7.38 (m, 7 H), 7.80−7.85 (m, 1 H), 7.95 (s, 1 H), 8.28 (d, J = 7.6 Hz, 1 H), 9.16 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{31}H_{27}N_2O_4$ (MH^+), 491.1966; found, 491.1942. HPLC (method 1, 95%; method 2, 96%).

3-Hydroxy-2-((1-(isopropoxycarbonyl)-1*H*-indol-3-yl)methyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (99): fluffy beige solid, 13%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (d, J = 6.1 Hz, 6 H), 1.73−1.86 (m, 4 H), 2.77 (t, J = 5.7 Hz, 2 H), 3.16 (t, J = 5.8 Hz, 2 H), 4.30 (s, 2 H), 5.15 (qt, 1 H), 7.04 (d, J = 8.8 Hz, 1 H), 7.23 (td, J = 7.5, 1.1 Hz, 1 H), 7.30 (td, J = 7.7, 1.3 Hz, 1 H), 7.63 (s, 1 H), 7.84 (d, J = 7.1 Hz, 1 H), 8.05 (d, J = 8.6 Hz, 1 H), 9.16 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{27}H_{27}N_2O_5$ (MH^+), 459.1915; found, 459.1902. HPLC (method 1, 96%; method 2, 100%).

Triethylammonium 2-((1-Acetyl-1*H*-indol-3-yl)methyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylate (100): fluffy beige solid, 5.3%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, J = 7.3 Hz, 9 H), 1.72−1.84 (m, 4 H), 2.61 (s, 3 H), 2.77 (t, J = 5.8 Hz, 2 H), 3.07 (q, J = 7.1 Hz, 6 H), 3.14 (t, J = 5.7 Hz, 2 H), 4.32 (s, 2 H), 7.04 (d, J = 8.8 Hz, 1 H), 7.23 (td, J = 7.4, 1.4 Hz, 1 H), 7.27 (td, J = 7.6, 1.5 Hz, 1 H), 7.74 (s, 1 H), 7.83 (dd, J = 7.1, 1.3 Hz, 1 H), 8.28 (d, J = 8.1 Hz, 1 H), 9.16 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{25}H_{23}N_2O_4$ (MH^+), 415.1653; found, 415.1645. HPLC (method 1, 100%; method 2, 100%).

2-(4-Chlorobenzyl)-3-methoxy-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-4-carboxylic Acid (108): A mixture of **31** (65 mg, 0.177 mmol), iodomethane (33 μL, 0.53 mmol), and potassium carbonate (74 mg, 0.71 mmol) was stirred in 2 mL of acetone at 25 °C for 16 h. The solid was removed by filtration. The reaction mixture was concentrated to give an oily residue. NaOH (aq 5 N) in the amount of 0.5 mL was added to the resulting residue, and the mixture was stirred at 25 °C for 16 h. The reaction mixture was acidified with HCl (aq 1 N) to pH ∼1. Concentration of the mixture gave an oily residue that was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and then converted back to the free acid as described above to yield **108** (50 mg, 74%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.69−1.94 (m, 4 H), 2.76−2.88 (m, 2 H), 3.11−3.19 (m, 2 H), 3.80 (s, 3 H), 4.21 (s, 2 H), 7.15 (d, J = 8.6 Hz, 1 H), 7.31 (s, 4 H), 7.49 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{20}ClNO_3$ (MH^+), 382.12045; found, 382.1207. HPLC (method 1, 96%; method 2, 97%).

Benzyl 3-(Benzyloxy)-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylate (113): A mixture of **31** (65 mg, 0.177 mmol), benzyl bromide (63 μL, 0.53 mmol), and potassium carbonate (74 mg, 0.71 mmol) was stirred in 2 mL of acetone at 25 °C for 16 h. Concentration of the mixture gave an oily residue that was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and then converted back to the free acid as described above to yield **113** (71 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.67−1.91 (m, 4 H), 2.87 (t, J = 6.3 Hz, 2 H), 3.11 (t, J = 6.0 Hz, 2 H), 4.30 (s, 2 H), 4.96 (s, 2 H), 5.49 (s, 2 H), 7.07−7.59 (m, 16 H). Anal. ($C_{35}H_{30}ClNO_3$) C, H, N. HRMS (ESI$^+$) calcd for $C_{35}H_{30}ClNO_3$ (MH^+), 548.1987; found, 548.19905.

3-(Benzyloxy)-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-4-carboxylic Acid (109): A mixture of **113** (100 mg, 0.182 mmol) and 10 N NaOH (1 mL) was heated in 2 mL of ethanol at 105 °C for 3 h. The reaction mixture was acidified with HCl (aq 1 N) to pH ~1. Concentration of the mixture gave an oily residue that was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and then converted back to the free acid as described above to yield **109** as a white solid (75 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77−1.92 (m, 4 H), 2.88 (t, J = 5.2 Hz, 2 H), 3.17 (t, J = 5.7 Hz, 2 H), 4.30 (s, 2 H), 5.04 (s, 2 H), 7.23−7.55 (m, 11 H). HRMS (ESI$^+$) calcd for $C_{28}H_{24}ClNO_3$ (MH^+), 458.1518; found, 458.1518. HPLC (method 1, 95%; method 2, 97%).

α-Oxo-(4-chlorobenzene)-propanenitrile (21): A mixture of 4-chlorophenylacetyl chloride (20, 9.54 g, 50 mmol) and trimethylsilyl cyanide (5.0 g, 50 mmol) was slowly heated to 120 °C for 4 h. Trimethylsilyl chloride was removed by distillation. The residue was distilled at reduced pressure to give the desired product (4.9 g, 55%) as a colorless oil. ^{1}H NMR (400 MHz, $CHCl_3$): δ 3.93−4.00 (s, 2 H), 7.30−7.34 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H).

***N*-[(2-Oxo-3-(4-chlorobenzene)-propyl]-acetamide (22):** A solution of α-oxo-(4-chlorobenzene)-propanenitrile (21, 0.34 g, 1.9 mmol) in acetic acid (2 mL)/acetic anhydride (2 mL) was added dropwise to a suspension of activated zinc dust (1.2 g, 19 mmol) in acetic acid (0.5 mL)/acetic anhydride (0.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The solid was removed by filtration. The solvents were evaporated under reduced pressure to provide a yellow solid. Recrystallization from ethyl acetate gave the desired product (0.38 g, 90%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83−1.89 (s, 3 H), 3.76−3.83 (s, 2 H), 4.02 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 8.17 (t, J = 8.0 Hz, 1 H). MS (electrospray): 224 ($M - H)^-$.

3-(Acetylamino)-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (111): Isatin **52** (0.15 g, 0.74 mmol) and acetamide **22** (0.2 g, 0.89 mmol) in 1 mL of KOH (aq, 6 N) and 1 mL of ethanol were heated at 100 °C for 1.5 h. The resulting beige solid was collected via filtration. At 0 °C, HCl (aq, 1 N) was added to the solid until pH ~1. The resulting suspension was stirred at 25 °C for 0.5 h. The light yellow solid (0.15 g, 50%) was collected via filtration. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76−1.93 (m, 4 H), 1.98−2.07 (s, 3 H), 2.83−2.95 (m, 2 H), 3.13−3.23 (m, 2 H), 4.17−4.25 (s, 2 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.28−7.37 (m, 4 H), 7.62 (d, J = 8.0 Hz, 1 H), 9.79−9.92 (s, 1 H), 13.60−13.97 (br s, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{21}ClN_2O_3$ (MH^+), 409.13135; found, 409.1308. HPLC (method 1, 97%; method 2, 99%).

3-Amino-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (110): Compound **111** (90 mg, 0.22 mmol) was suspended in 1.5 mL of HCl (aq, 1 N). The mixture was stirred in microwave reactor at 110 °C for 40 min. Concentration of the reaction mixture gave an oily residue. HPLC of the residue under basic conditions afforded a white solid, which was acidified at 0 °C with 1 N aq HCl to pH ~1. The precipitate was collected by filtration, washed with water, and dried under vacuum to yield **110** (7.5 mg, 9%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71−1.88 (m, 4 H), 2.73−2.84 (m, 2 H), 3.02−3.13 (m, 2 H), 3.17 (d, J = 4.0 Hz, 2 H), 4.05−4.15 (d, J = 8.0 Hz, 1 H), 4.25−4.32 (s, 2 H), 7.14 (d, J = 8.0 Hz, 1 H), 7.32−7.39 (s, 4 H), 8.00 (d, J = 8.0 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{19}ClN_2O_2$ (MH^+), 367.12078; found, 367.1212. HPLC (method 1, 95%; method 2, 95%).

3-(Benzoylamino)-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (112): Compound **110** (37 mg, 0.1 mmol), benzoyl chloride (12.7 μL, 0.11 mmol), and triethylamine (15.3 μL, 0.11 mmol) in 1 mL THF were stirred at 25 °C for 16 h. Concentration of the reaction mixture gave an oily residue. HPLC of the residue under basic conditions afforded a white solid, which was acidified at 0 °C with 1 N aq HCl to pH ~1. The precipitate was collected by filtration, washed with water, and dried under vacuum to yield **112** (4.6 mg, 9%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD): δ 2.08−2.22 (m, 4 H), 3.13−3.20 (m, 2 H), 3.48−3.53 (m, 2 H), 4.54−4.60 (s, 2 H), 7.38−7.41 (s, 3 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.69−7.86 (m, 4 H), 7.97 (d, J = 8.0 Hz, 1 H), 8.09−8.15 (m, 2 H). HRMS (ESI$^+$) calcd for $C_{28}H_{23}ClN_2O_3$ (MH^+), 471.14700; found, 471.147. HPLC (method 1, 100%; method 2, 100%).

***N*-Alkylated Derivatives of 24. General Procedure IX**. A mixture of **24** (0.12 g, 0.297 mmol), triethylamine (46 μL, 0.30 mmol), $NaCNBH_3$ (23 mg, 0.36 mmol), 3 mL of methanol, 3 drops of acetic acid, and the appropriate aldehyde or ketone (0.446 mmol) were stirred at 25 °C overnight. Water and triethylamine were added dropwise to dissolve the precipitate. The clear reaction mixture was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and then converted back to the free acid as described above.

2-(4-Chlorobenzyl)-9-ethyl-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (114): light yellow solid, 3.4%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (t, J = 7.3 Hz, 3 H), 2.55−2.60 (m, 1 H), 2.66−2.76 (m, 1 H), 3.34 (q, J = 7.3 Hz, 2 H), 3.64−3.93 (m, 2 H), 4.30 (s, 2 H), 4.40 (d, J = 15.2 Hz, 1 H), 4.62 (d, J = 15.2 Hz, 1 H), 7.26−7.34 (m, 3 H), 7.34−7.41 (m, 2 H), 9.08 (d, J = 8.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{21}ClN_2O_3$ (MH^+), 397.13135; found, 397.1334. HPLC (method 1, 95%; method 2, 98%).

2-(4-Chlorobenzyl)-3-hydroxy-9-isopropyl-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (115): white solid, 32%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43 (d, J = 6.6 Hz, 6 H), 3.30−3.48 (m, 2 H), 3.61−3.92 (m, 3 H), 4.38−4.61 (m, 4 H), 7.21−7.32 (m, 3 H), 7.39 (d, J = 8.3 Hz, 2 H), 9.32 (d, J = 9.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{23}ClN_2O_3$ (MH^+), 411.14700; found, 411.1465. HPLC (method 1, 97%; method 2, 98%).

9-Benzyl-2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (116): white solid, 40%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.32−3.54 (m, 2 H), 3.67−3.96 (m, 2 H), 4.29 (s, 2 H), 4.38−4.47 (m, 2 H), 4.52 (s, 2 H), 7.21 (d, J = 8.8 Hz, 1 H), 7.24−7.33 (m, 2 H), 7.34−7.43 (m, 2 H), 7.48−7.57 (m, 3 H), 7.56−7.67 (m, 2 H), 9.31 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{27}H_{23}ClN_2O_3$ (MH^+), 459.14700; found, 459.147. HPLC (method 1, 95%; method 2, 98%).

9-Acetyl-2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (117): To a mixture of **24** (0.14 g, 0.346 mmol) in 2 mL of pyridine was added triethylamine (60 μL, 0.43 mmol) and acetic anhydride (0.18 mL, 2.07 mmol) at 0 °C. The reaction mixture was warmed to 25 °C and stirred overnight. HPLC of the reaction mixture afforded the acetamide ethyl ester (90 mg, 0.20 mmol) as a white solid, which was treated with LiOH (36 mg, 0.80 mmol) in 1 mL of water. The mixture was stirred at 25 °C for 5 h. DMSO and triethylamine were added to the reaction mixture dropwise to dissolve the precipitate. HPLC of the clear solution gave a yellow solid, **117** (20.7 mg, 25%), as a mixture of two isomers. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3 H), 3.21−3.42 (m, 2 H), 3.77−3.87 (m, 2 H), 4.34 (s, 2 H), 4.73−4.84 (m, 2 H), 7.27−7.42 (m, 5 H), 8.49−8.57 (m, 1 H). HRMS (ESI$^+$) calcd for $C_{22}H_{19}ClN_2O_4$ (MH^+), 411.11061; found, 411.1097. HPLC (method 1, 95%; method 2, 97%).

9-(Aminocarbonyl)-2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (119): A mixture of **24** (0.213 g, 0.53 mmol), acetic acid (0.6 mL, 5.3 mmol), triethylamine (0.146 mL, 1.06 mmol), KOCN (43 mg, 0.53 mmol), and pyridine (0.84 mL, 5.3 mmol) was stirred at 25 °C overnight. The solid was removed by filtration. HPLC of the mother liquor gave **119** (49.1 mg, 22%) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.25 (m, 2 H), 3.68 (m, 2 H), 4.34 (s, 2 H), 4.63 (s, 2 H), 7.22−7.45 (m, 5 H), 8.47 (d, J = 9.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{18}ClN_3O_4$ (MH^-), 410.09131; found, 410.0921. HPLC (method 1, 95%; method 2, 97%).

General Procedure X for the Synthesis of *N*-Amide Derivatives of 24, C-3 Esters, and C-3 Carbonates of 31: To **24** or **31** (0.32 mmol) in 2 mL of dichloromethane at 0 °C was added the appropriate carbonyl chloride, sulfonyl chloride, or chloroformate

(0.48 mmol) and triethylamine (0.10 mL, 0.74 mmol). The mixture was stirred at 25 °C overnight. The crude mixture was purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine) and then converted back to the free acid as described above.

3-Acetoxy-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (101): yellow solid, 24%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72−1.93 (m, 4 H), 2.90 (t, J = 5.6 Hz, 2 H), 3.19(t, J = 5.6 Hz, 2 H), 4.20 (s, 2 H), 7.29−7.37 (m, 4 H), 7.39 (d, J = 8.6 Hz, 1 H), 7.70 (d, J = 8.8 Hz, 1 H). Anal. ($C_{22}H_{20}ClNO_4 \cdot 0.2H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{22}H_{20}ClNO_4$ (MH$^+$), 410.11537; found, 410.11566.

2-(4-Chlorobenzyl)-3-(pivaloyloxy)-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (102): yellow solid, 16%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.28 (s, 9 H), 1.76−1.89 (m, 4 H), 2.86 (t, J = 5.1 Hz, 2 H), 3.15 (t, J = 5.4 Hz, 2 H), 4.04 (s, 2 H), 7.19−7.28 (m, 3 H), 7.30−7.36 (m, 2 H), 7.65 (d, J = 8.6 Hz, 1 H). Anal. ($C_{26}H_{26}ClNO_4 \cdot H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{26}H_{26}ClNO_4$ (MH$^+$), 452.16232; found, 452.16258.

2-(4-Chlorobenzyl)-3-(thiophene-2-carbonyloxy)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (103): white solid, 40%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75−1.95 (m, 4 H), 2.86 (t, J = 5.7 Hz, 2 H), 3.20 (t, J = 5.5 Hz, 2 H), 4.12 (s, 2 H), 7.16−7.38 (m, 6 H), 7.67−7.78 (m, 1 H), 7.95 (br s, 1 H), 8.04−8.17 (m, 1 H). Anal. ($C_{26}H_{20}ClNO_4S \cdot H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{26}H_{20}ClNO_4S$ (MH$^+$), 478.08744; found, 478.08784.

3-(Benzoyloxy)-2-(4-chlorobenzyl)-7,8,9,10-tetrahydrobenzo-[*h*]quinoline-4-carboxylic Acid (104): pale yellow solid, 36%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80−1.94 (m, 4 H), 2.92 (t, J = 5.1 Hz, 2 H), 3.23 (t, J = 6.1 Hz, 2 H), 4.26 (s, 2 H), 7.17−7.24 (m, 2 H), 7.24−7.32 (m, 2 H), 7.42 (d, J = 8.8 Hz, 1 H), 7.65 (t, J = 7.7 Hz, 2 H), 7.75 (d, J = 8.6 Hz, 1 H), 7.81 (t, J = 7.5 Hz, 1 H), 8.09 (dd, J = 8.5, 1.14 Hz, 2 H). Anal. ($C_{28}H_{22}ClNO_4 \cdot H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{28}H_{22}ClNO_4$ (MH$^+$), 472.13102; found, 472.13137.

2-(4-Chlorobenzyl)-3-(cyclohexanecarbonyloxy)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (105): pale yellow solid, 61%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30−1.52 (m, 2 H), 1.69−1.78 (m, 2 H), 1.84 (d, J = 5.8 Hz, 4 H), 1.92−2.03 (m, 2 H), 2.60−2.71 (m, 1 H), 2.90 (t, J = 5.9 Hz, 2 H), 3.18 (t, J = 5.9 Hz, 2 H), 3.27−3.41 (m, 4 H), 4.19−4.20 (m, 2 H), 7.24−7.30 (m, 2 H), 7.32−7.37 (m, 2 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.66 (d, J = 8.6 Hz, 1 H). Anal. ($C_{28}H_{28}ClNO_4 \cdot 0.3H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{28}H_{28}ClNO_4$ (MH$^+$), 478.17797; found, 478.17829.

2-(4-Chlorobenzyl)-3-(methoxycarbonyloxy)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (106): pale yellow solid, 12%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76−1.91 (m, 4 H), 2.85 (t, J = 5.5 Hz, 2 H), 3.17 (t, J = 5.435 Hz, 2 H), 3.75 (s, 3 H), 4.11 (s, 2 H), 7.20 (d, J = 8.6 Hz, 1 H), 7.24−7.30 (m, 2 H), 7.29−7.36 (m, 2 H), 7.72 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{20}ClNO_5$ (MH$^+$), 426.11028; found, 426.10999. HPLC (method 1, 95%; method 2, 96%).

2-(4-Chlorobenzyl)-3-(isobutoxycarbonyloxy)-7,8,9,10-tetrahydrobenzo[*h*]quinoline-4-carboxylic Acid (107): pale yellow solid, 21%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (d, J = 6.6 Hz, 6 H), 1.77−1.88 (m, 4 H), 1.88−1.97 (m, 1 H), 2.86 (t, J = 5.6 Hz, 2 H), 3.17 (t, J = 5.6 Hz, 2 H), 3.91 (d, J = 6.8 Hz, 2 H), 4.11 (s, 2 H), 7.17−7.40 (m, 5 H), 7.71 (d, J = 8.6 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{26}H_{26}ClNO_5$ (MH$^+$), 468.15723; found, 468.15703. HPLC (method 1, 96%; method 2, 96%).

9-Benzoyl-2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (118): yellow solid, 10%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.32 (dd, J = 5.8, 5.8 Hz, 2 H), 3.81−3.83 (m, 2 H), 4.34 (s, 2 H), 4.81 (s, 2 H), 7.27−7.34 (m, 3 H), 7.35−7.41 (m, 2 H), 7.43−7.54 (m, 5 H), 8.52 (d, J = 8.9 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{27}H_{21}ClN_2O_4$ (MH$^+$), 473.12626; found, 473.1261. HPLC (method 1, 95%; method 2, 99%).

2-(4-Chlorobenzyl)-9-(ethoxycarbonyl)-3-hydroxy-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (120): white solid, 5%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (t, J = 7.1 Hz, 3 H), 3.25 (dd, J = 5.7, 6.2 Hz, 2 H), 3.73 (dd, J = 5.7, 6.2 Hz, 2 H), 4.12 (t, J = 7.1 Hz, 2 H), 4.32 (s, 2 H), 4.67 (s, 2 H), 7.30−7.42 (m, 5 H), 8.37 (d, J = 8.84 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{21}ClN_2O_5$ (MH$^+$), 441.12118; found, 441.1202. HPLC (method 1, 97%; method 2, 97%).

2-(4-Chlorobenzyl)-3-hydroxy-9-(methylsulfonyl)-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (121): yellow solid, 8%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.97 (s, 3 H), 3.34 (dd, J = 5.7, 6.1 Hz, 2 H), 3.53 (dd, J = 5.7, 6.1 Hz, 2 H), 4.27 (s, 2 H), 4.45 (s, 2 H), 7.25 (d, J = 8.8 Hz, 1 H), 7.31 (m, 2 H), 7.37 (m, 2 H), 8.97 (d, J = 8.8 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{19}ClN_2O_5S$ (MH$^+$), 447.07760; found, 447.0763. HPLC (method 1, 97%; method 2, 98%).

2-(4-Chlorobenzyl)-3-hydroxy-9-(isopropylsulfonyl)-7,8,9,10-tetrahydro-1,9-phenanthroline-4-carboxylic Acid (122): yellow solid, 3.5%; mixture of two isomers in a 2:1 ratio. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.23 (d, J = 7.0 Hz, 6 H), 3.11−3.14 (m, 2 H), 3.23−3.32 (septlet, J = 5.0 Hz, 1 H), 3.56 (dd, J = 6.0, 6.0 Hz, 0.6 H), 3.63 (dd, J = 6.0, 6.0 Hz, 1.4 H), 4.25 (s, 2 H), 4.46 (s, 0.6 H), 4.53 (s, 1.4 H), 7.23−7.27 (m, 1 H), 7.28 (d, J = 10.0 Hz, 2 H), 7.33 (d, J = 10.0 Hz, 2 H), 8.78−8.87 (m, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{23}ClN_2O_5S$ (MH$^+$), 475.10890; found, 475.1085. HPLC (method 1, 95%; method 2, 97%).

3-Hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic Acid (37): The procedure described by Cragoe and Robb[60] was followed, reacting 7-(trifluoromethyl)indoline-2,3-dione (**35**) with bromopyruvic acid (**36**). The crude acid was purified by method A (when it was taken up in the chromatography solvent to absorb onto silica gel, a large amount of yellow precipitate appeared; this was found to be a mixture of unknown side products and was filtered out and discarded), taking the purified product up in 5% acetonitrile in water before acidifying to pH 1 with concentrated hydrochloric acid to precipitate the free acid to give an ivory-colored powder, 33%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (t, 1 H), 7.99 (d, J = 7.3 Hz, 1 H), 8.31 (d, J = 8.3 Hz, 1 H), 8.87 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{11}H_7F_3NO_3$ (MH$^+$), 258.0373; found, 258.0373.

Methyl 3-Hydroxy-8-(trifluoromethyl)quinoline-4-carboxylate (38): The acid chloride of **37** was prepared as described above for the synthesis of benzyl chloromethyl ketones (General Procedures, method A). The solution was stirred for 1 h at room temperature after the addition of oxalyl chloride, then quenched by addition of an equal volume of methanol. Stirring was continued for an additional hour; the solution was then evaporated and purified by flash chromatography over silica gel (10−20% ethyl acetate in hexanes), 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (s, 3 H), 7.65 (t, J = 8.1 Hz, 1 H), 7.93 (d, J = 7.3 Hz, 1 H), 8.90 (d, J = 8.8 Hz, 1 H), 8.94 (s, 1 H), 11.66 (s, 1 H). MS (electrospray): 270 (M − H)$^-$.

Methyl 2-Bromo-3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylate (39): In a 100 mL two-necked round-bottomed flask fitted with a condenser **38** (1.05 g, 3.86 mmol) was taken up in 16 mL of tetrahydrofuran, and *N*-bromosuccinimide was added (0.275 g, 1.54 mmol, 0.4 equiv). The mixture was heated at reflux, adding an additional 0.4 equiv NBS every hour until LC-MS analysis showed that the ratio of product to starting material was no longer increasing (4 h). The reaction mixture was then cooled, partitioned between 1 M aqueous hydrochloric acid and ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by flash chromatography over silica gel (25% ethyl acetate in hexanes) to give a 27% yield of pure product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (s, 3 H), 7.67 (t, J = 8.1 Hz, 1 H), 7.93 (d, J = 7.1 Hz, 1 H), 8.84 (d, J = 8.8 Hz, 1 H), 12.38 (s, 1 H). MS (electrospray): 348 (M − H)$^-$.

2-(4-Chlorophenylamino)-3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic Acid (34): Introduction of the 4-chloroaniline moiety was achieved by subjecting **39** to a modification of the microwave-assisted Pd-catalyzed coupling protocol described by Skjaerbaek et al.[61] We had to use considerably more aniline (4 equiv), Pd catalyst (20 mol %), and ligand (40 mol %) to achieve a synthetically useful degree of conversion to our desired product. The major side product was formed by debromination at the 2-position of the quinoline. The crude methyl ester (**40**) was not

purified, but was taken up in tetrahydrofuran, methanol, and 1 M aqueous sodium hydroxide and refluxed until LC-MS analysis showed complete hydrolysis of the ester (18 h). The reaction mixture was then cooled, acidified by addition of 2 M aqueous hydrochloric acid, extracted into ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by preparative HPLC (water/acetonitrile with 0.1% triethylamine). A second preparative HPLC purification gave pure product, which was lyophilized to a fluffy, off-white solid, 1.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, J = 7.2 Hz, 9 H), 3.10 (dq, J = 7.2, 4.8 Hz, 6 H), 7.25 (t, 1 H), 7.32 (dt, 2 H), 7.52 (dd, J = 7.5, 1.4 Hz, 1 H), 8.29 (dt, 2 H), 8.86 (s, 1 H), 9.19 (s, 1 H), 9.40 (dd, J = 8.5, 1.1 Hz, 1 H). HRMS (ESI$^+$) calcd for $C_{17}H_{11}F_3N_2O_3$ (MH^+), 383.0405; found, 383.0387. HPLC (method 1, 96%; method 2, 99%).

2-(4-Chlorophenyl)-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)-acetamide (44): To a solution of 5,6,7,8-tetrahydronaphthalen-1-amine (5 g, 34 mmol) and diisopropyl ethylamine (7.1 mL, 41 mmol) in 120 mL of dichloromethane at 0 °C was added 2-(4-chlorophenyl)acetyl chloride (7.1 g, 37.4 mmol). The reaction was stirred at room temperature overnite. The next day the reaction mixture was washed with 1 N HCl, followed by water. The organic layer was washed with brine and dried over magnesium sulfate to give **44** (9.1 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.65−1.72 (m, 4 H), 2.71 (s, 2 H), 3.34 (s, 2 H), 3.66 (s, 2 H), 6.90 (d, J = 7.07 Hz, 1 H), 7.03 (t, J = 7.71 Hz, 1 H), 7.15 (d, J = 7.58 Hz, 1 H), 7.34−7.42 (m, 4 H), 9.36 (s, 1 H).

Ethyl 2-(4-Chlorobenzyl)-4-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-3-carboxylate (47): To a 50 mL round-bottom flask under an N_2 atmosphere were added 2-(4-chlorophenyl)-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)acetamide **44** (0.300 g, 1.0 mmol, 1.0 equiv) and PCl_5 (0.230 g, 1.1 mmol, 1.1 equiv). The mixture was heated to 65 °C in an oil bath for 4 h. The resulting mixture was then allowed to cool to room temperature, and all the volatiles were removed in vacuo to provide the intermediate (*E*)-2-(4-chlorophenyl)-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)acetimidoyl chloride **45**, which was carried on crude.

In a separate 50 mL round-bottom flask under nitrogen atmosphere was added sodium hydride as a 60% suspension in mineral oil (0.048 g, 1.2 mmol, 1.0 equiv) and 20 mL of toluene. To this was added diethyl malonate (0.160 g, 1.0 mmol 1.0 equiv). This mixture was allowed to stir at room temperature for 1 h, at which point it was heated to 110 °C, and the crude (*E*)-2-(4-chlorophenyl)-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)acetimidoyl chloride was added. The mixture was allowed to reflux for 15 h. Upon cooling to room temperature, the mixture was quenched with 1 mL of water and then poured into 100 mL of water. The aqueous layer was extracted with three 50 mL portions of ethyl acetate, and the combined organic layers were washed with water and brine and dried over magnesium sulfate. The resulting material was purified by silica gel chromatography (25−50% ethyl acetate in hexanes) to give the intermediate diethyl 2-(2-(4-chlorophenyl)-1-(5,6,7,8-tetrahydronaphthalen-1-ylamino)ethylidene)malonate **46**. This was then heated neat in an oil bath to 150 °C for 6 h under a mild vacuum. The resulting solid was triturated with petroleum ether and then dried in vacuo. Further purification by silica gel chromatography (25% ethyl acetate in hexanes) gave the desired product **47** as a tan powdery solid (0.030 g, 8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.07 Hz, 3 H), 1.70−1.92 (m, 4 H), 2.46 (s, 52 H), 2.70−2.92 (m, 2 H), 4.22 (s, 2 H), 4.34 (q, J = 7.07 Hz, 2 H), 7.01 (d, J = 8.08 Hz, 1 H), 7.21−7.28 (m, 2 H), 7.29−7.40 (m, 2 H), 8.02 (d, J = 8.34 Hz, 1 H), 8.21 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{23}H_{22}ClNO_3$ (MH^+), 396.1361; found, 396.1347.

2-(4-Chlorobenzyl)-4-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]-quinoline-3-carboxylic Acid (41): To a 25 mL round-bottom flask was added ethyl 2-(4-chlorobenzyl)-4-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]quinoline-3-carboxylate **47** (0.025 g, 0.06 mmol, 1.0 equiv) and 10 mL of 1.0 N $LiOH_{(aq)}$. Methanol in the amount of 3 mL and 3 mL of THF were added to aid solubility. The resulting solution was stirred at room temperature for 16 h. The mixture was then poured into 50 mL 1.2 N $HCl_{(aq)}$ and extracted with three 25 mL portions of ethyl acetate. The combined organic layers were washed with water and brine and dried over magnesium sulfate. Filtration and evaporation of solvent gave the desired product as a white solid (0.017 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65−1.91 (m, 4 H), 2.22−2.37 (m, 2 H), 2.87 (t, J = 5.94 Hz, 2 H), 4.91 (s, 2 H), 7.21 (d, J = 8.34 Hz, 1 H), 7.31 (d, J = 8.08 Hz, 2 H), 7.47 (d, J = 8.34 Hz, 2 H), 8.11 (d, J = 8.34 Hz, 1 H), 8.58 (s, 1 H). HRMS (ESI$^+$) calcd for $C_{21}H_{18}ClNO_3$ (MH^+), 368.1048; found, 368.1045. HPLC (method 1, 100%; method 2, 100%).

NMR Experiments: The NMR samples were prepared in D_2O buffer with 20 mM imidazole, pH = 7.4, 150 mM NaCl, 5 mM $CaCl_2$, and 0.02% NaN_3. Titrations were performed with a 100 μM nominal concentration of compound, and the monomeric form of P-selectin was added at different ratios. The STD experiments were performed with a 100 μM nominal concentration of compound and 3 μM of the dimeric form of P-selectin (P-selectin Ig chimera). All experiments were performed at 25 °C in a Bruker Avance equipped with cryoprobe. For the STD experiment, on-resonance saturation was at 0.5 ppm and off-resonance was at −10 ppm. The saturation was performed with a 50 ms Gaussian-shaped pulse for 2 s. Data were processed with Bruker software Xwinnmr. Control STD experiments were performed with only the compound present in the sample.

Pharmacokinetic Studies: The animals used in the pharmacokinetic (PK) studies were male adult C57 mice, Sprague−Dawley rats and Beagle dogs (Charles River Laboratories, Wilmington, MA). All the PK studies were performed at Wyeth Research Laboratory (Andover, MA) under the supervision of the Institutional Animal Care and Use Committee. As a result of low solubilities for test articles, organic solvents were used for IV administration. The dose formulation for intravenous administration was 20% DMSO/80% poly(ethylene glycol) 400 (PEG 400, v/v, 5 mL/kg) for mice, 50% DMSO/50% PEG 400 (v/v, 1 mL/kg) for rats, and 100% DMSO (0.05 mL/kg) for dogs, respectively. The oral dose formulation was an aqueous suspension containing 2% polysorbate 80 (aka tween 80) and 0.5% methylcellulose for mice, rats, and dogs. Blood samples of approximately 0.25 mL were collected into K_2EDTA coated sampling tubes at 0.083, 0.25, 0.5, 1, 2, 4, 7, and 24 h post dose administration. Plasma samples were harvested and stored at −80 °C until analysis.

In a 0.5 mL 96-well plate, 50 μL of plasma sample was precipitated with 100 μL acetonitrile containing 500 ng/mL of internal standard. The internal standard is a compound with similar chemical structure as that for test article. The samples were vertexed and centrifuged at 5700 rpm for 10 min. Supernatants were subjected to LC-MS/MS analysis. HPLC separation was performed on a Perkin-Elmer series 200 HPLC system (Perkin-Elmer, Norwalk, CT) using an XTerra MS C18 column (2.1 × 20 mm, 2.5 μm; Waters, Milford, MA). The detection of test articles was performed on a PESCIEX API-3000 triple quadrupole mass spectrometer (Applied Biosystems, Concord, Ontario, L4K4V8) using TurboIon Spray source. Plasma standard curves were generated by plotting the peak area ratio of the test article and the internal standard against nominal concentrations.

The pharmacokinetic parameters were determined using WinNonlin (version 4.1, Pharsight, Mountain View, CA). Calculations were performed using the noncompartmental analysis approach. The estimation of area under the plasma concentration versus time curve (AUC) was based upon the log trapezoidal rule. The terminal rate constant (λ) was derived from the slope of the terminal log-linear phase of plasma concentrations−time curves. The apparent terminal half-life ($t_{1/2}$) was calculated as 0.693/λ. No statistical analysis other than descriptive statistics was conducted.

Biology: Biacore P-Selectin/PSGL-1 Inhibition Assay. Surface plasmon resonance (Biacore) assays were performed on a Biacore 3000 instrument (Biacore, Inc., Piscataway, NJ) at 25 °C and at a flow rate of 30 μL/minute and consisted of 60-second equilibration, 60 μL sample injection (kinject), and 300-second dissociation. Due to the rapid and complete dissociation of P-selectin, the sensogram returned to baseline immediately following the end of each injection (see Figure 7). Previous studies showed that there was little change

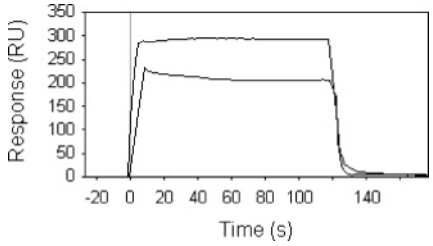


Figure 7. Representative sensogram showing double reference subtracted signals from P-selectin (P.LE) binding to immobilized PSGL-1 (19ek) in the presence (lower trace) and absence (upper trace) of antagonist. Plot prepared using Scrubber-2 software, Center for Biomolecular Interaction Analysis, David Myszka, University of Utah.

Table 14. Sample Order

sample ID	antagonist concentration (μM)
buffer blank	not applicable
P.LE uninhibited	not applicable
glycyrrhizin	1000
antagonist	250
antagonist	125
antagonist	62.5
antagonist	31.25
buffer blank	not applicable
P.LE uninhibited	not applicable

in the amount of uninhibited binding over a 24-hour period of sample injections. However, because no regeneration step was included, a 1× Biacore assay buffer "blank" injection and "uninhibited" 500 nM P.LE solution without small molecule antagonist bracketed every five sample injections. These bracketing controls were used in the analysis (see Table 14 and Biacore analysis section).

A purified, monomeric, truncated form of human PSGL-1, "19ek", which contains all the necessary P-selectin binding determinants,[62,63] was biotinylated via amine chemistry (Sulfo-NHS-LC-Biotin, Peirce) at a unique C-terminal lysine residue[43] and immobilized on a Biacore SA sensor chip (Biacore, Inc.), using HBS-EP buffer (Biacore, Inc.), target 600−700 RU. The coated chip was re-equilibrated with HBS-P buffer (Biacore, Inc.) to which 1 mM $CaCl_2$ and 1 mM $MgCl_2$ (both from Fisher) were added to ensure sufficient calcium for the calcium-dependent interaction of receptor and ligand. Compound **31** was incubated for 1 h in 1.1× Biacore assay buffer. The solution was centrifuged at 2500 g for 7 min through a 96 well 0.2 mM filter plate (Millipore). In validation of this filtration step (data not shown), a structurally varied subset of compounds that showed apparent solubility in the assay conditions showed no change in antagonist activity in the Biacore assay when a direct comparison was made between filtered and unfiltered samples. When test compounds showed visible precipitate prior to filtering, this was noted. The only inhibitions reported were those at concentrations free of precipitate.

Glycyrrhizin trisodium salt (TCI) was prepared as a positive control in parallel with our P-selectin antagonist in the same manner. Glycyrrhizin, a demonstrated antagonist of P-selectin (John T. Patton, GlycoTech Corporation, written communication, May 2000), has been shown to inhibit the P-selectin/PSGL-1 interaction with an IC_{50} of 1 mM in this assay. A soluble recombinant truncated form of human P-selectin, P-LE, comprised of the lectin and EGF domains, expressed in CHO cells[43] was added to each filtered small molecule solution. Final concentrations of reagents were 500 nM P.LE, 31.25 mM to 250 μM **31** (or 1 mM glycyrrhizin), 10% DMSO, and 1× Biacore buffer (100 mM HEPES, 150 mM NaCl, 1 mM $CaCl_2$, and 1 mM $MgCl_2$ (all reagents from Fisher), pH 7.4). Test samples were supplied to the Biacore instrument in a 96-well plate.

Biacore Data Analysis: The Biacore raw data file was exported as a text file to an Excel spreadsheet, where the buffer blanks bracketing the samples were averaged for each Fc, and subtracted from the averaged uninhibited P.LE samples and from all the other samples. Then the reference signal from Fc1 (uncoated) was subtracted from its corresponding active (coated) signal for each injection, a process known as double referencing.[64] The percent inhibition of binding was calculated by dividing the reference subtracted inhibited signal by the reference subtracted uninhibited signal, subtracting this value from 1, then multiplying by 100. The replicate percent inhibition values were averaged and expressed as the mean ± standard deviation. The interexperiment standard deviation of calculated percent inhibitions in the Biacore assay was ±5. The standard deviation between percent inhibitions calculated for two injections within the same assay was very low, less than 1.

Rat Carotid Balloon Injury Model. Male Sprague−Dawley rats underwent angioplasty of the left carotid artery by the intraluminal passage of a balloon catheter. Rats were treated orally with vehicle or **31** at 30 mg/kg formulated in methylcellulose/Tween 1 h before surgery and once/day for 13 days following surgery. Histology was performed in the carotid arteries 14 days after injury. Tissue sections from the artery were stained, and the intimal and the medial areas were then quantified on images taken using image analysis software programs. Results were expressed as the ratio of the intimal areas to the medial areas.

APO E Knockout Model. Six-week-old male Apo E −/− mice were administered vehicle or **31** at 100 mg/kg/day mixed in their normal chow and offered ad libitum for 20 weeks. After 20 weeks of treatment, quantitative analysis of atherosclerotic lesions was performed at the aortic sinus. Tissue sections were stained and images were taken to quantify the lesions.

Acknowledgment. We would like to thank Yuanhong Li from the Structural Biology group for her assistance with protein NMR, the Discovery Analytical Chemistry group for spectral data, and the Discovery Synthetic Chemistry and Chemical Development groups for scaleup of compound **31**.

Supporting Information Available: Movies of leukocyte rolling in cremasteric postcapillary venules for untreated mice and **31** treated mice. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) McEver, R. P.; Cummings, R. D. Role of PSGL-1 binding to selectins in leukocyte recruitment. *J. Clin. Invest.* **1997**, *100*, S97−103.
(2) Furie, B.; Furie, B. C.; Flaumenhaft, R. A journey with platelet P-selectin: the molecular basis of granule secretion, signaling, and cell adhesion. *Thromb. Haemostasis* **2001**, *86*, 214−221.
(3) Lowe, B. Glycosylation in the control of selectin counter-receptor structure and function. *Immunol. Rev.* **2002**, *186*, 19−36.
(4) Vestweber, D. Regulation of endothelial cell contacts during leukocyte extravasation. *Curr. Opin. Cell Biol.* **2002**, *14*, 587−593.
(5) Ley, K. The role of selectins in inflammation and disease. *Trends Mol. Med.* **2003**, *9*, 263−268.
(6) Coller, B. S. Leukocytosis and ischemic vascular disease morbidity and mortality: Is it time to intervene? *Arterioscler., Thromb., Vasc. Biol.* **2005**, *25*, 658−670.
(7) Blann, A. D.; Nadar, S. K.; Lip, G. Y. H. The adhesion molecule P-selectin and cardiovascular disease. *Eur. Heart J.* **2003**, *24*, 2166−2179.
(8) Hope, S. A. Cellular adhesion molecules and cardiovascular disease. Part II. Their association with conventional and emerging risk factors, acute coronary events and cardiovascular risk *Intern. Med. J.* **2003**, *33*, 450−462.
(9) Martins, P. da C.; van den Berk, N.; Ulfman, L. H.; Koenderman, L.; Hordijk, P. L.; Zwaginga, J. J. Platelet-monocyte complexes support monocyte adhesion to endothelium by enhancing secondary tethering and cluster formation. *Arterioscler., Thromb., Vasc. Biol.* **2004**, *24*, 193−199.
(10) Huo, Y.; Ley, K. Adhesion molecules and atherogenesis. *Acta Physiol. Scand.* **2001**, *173*, 35−43.
(11) Huo, Y.; Schober, A.; Forlow, B,; Smith, D. F.; Hyman, M. C.; Jung, S.; Littman, D. R. Weber, C.; Ley, K. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. *Nature Med.* **2003**, *9*, 61−67.
(12) Burger, P. C.; Wagner, D. D.; Platelet P-selectin facilitates atherosclerotic lesion development. *Blood* **2003**, *101*, 2661−2666.

(13) Bienvenu, J. G.; Tanguay, J.-F.; Theoret, J.-F.; Kumar, A.; Schaub, R. G.; Merhi, Y.; Recombinant soluble P-selectin glycoprotein ligand-1-lg reduces restenosis through inhibition of platelet-neutrophil adhesion after double angioplasty in swine. *Circulation* **2001**, *103*, 1128−1134.
(14) Smyth, S. S.; Reis, E. D.; Zhang, W.; Fallon, J. T.; Gordon, R. E.; Coller, B. S.; et al. Beta(3)-integrin-deficient mice but not P-selectin-deficient mice develop intimal hyperplasia after vascular injury: correlation with leukocyte recruitment to adherent platelets 1 h after injury. *Circulation* **2001**, *103*, 2501−2507.
(15) Myers, D.; Wrobleski, S.; Londy, F.; Fex, B.; Hawley, A.; Schaub, R.; Greenfield, L.; Wakefield, T. New and effective treatment of experimentally induced venous thrombosis with anti-inflammatory rPSGL-Ig. *Thromb. Haemostasis* **2002**, *87*, 374−382.
(16) Eppihimer, M. J.; Schaub, R. G. P-selectin-dependent inhibition of thrombosis during venous stasis. *Arterioscler., Thromb., Vasc. Biol.* **2000**, *20*, 2483−2488.
(17) Gasser, M.; Waaga-Gasser, A. M.; Grimm, M. W.; Grimm, M. R.; Lenhard, M. S.; Krist-Van Holthe, J. E.; Laskowski, I.; Shaw, G. D.; Thiede, A.; Hancock, W. W.; Tilney, N. L. Selectin blockade plus therapy with low-dose sirolimus and cyclosporin a prevent brain death-induced renal allograft dysfunction. *Am. J. Transplant.* **2005**, *5*, 662−670.
(18) Seekamp, A.; van Griensven, M.; Dhondt, E.; Diefenbeck, M.; Demeyer, I.; Vundelinckx, G.; Haas, N.; Schaechinger, U.; Wolowicka, L.; Rammelt, S.; Stroobants, J.; Marzi, I.; Brambrink, A. M.; Dziurdzik, P.; Gasiorowski, J.; Redl, H.; Beckert, M.; Khan-Boluki, J. The effect of anti-L-selectin (aselizumab) in multiple traumatized patients—Results of a phase II clinical trial. *Crit. Care Med.* **2004**, *32*, 2021−2028.
(19) (a) Alper, J. Searching for medicine's sweet spot. *Science* **2001**, *291*, 2338−2343. (b) Kerr, K. M.; Auger, W. R.; Marsh, J. J.; Comito, R. M.; Fedullo, R. L.; Smits, G. J.; Kapelanski, D. P.; Fedullo, P. F.; Channick, R. N.; Jamieson, S. W.; Moser, K. M. The use of cylexin (CY-1503) in prevention of reperfusion lung injury in patients undergoing pulmonary thromboendarterectomy. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 14−20.
(20) (a) Aydt, E.; Wolff, G. Development of synthetic pan-selectin antagonists: A new treatment strategy for chronic inflammation in asthma. *Pathobiology* **2003**, *70*, 297−301. (b) Romano, S. J., Selectin antagonists: Therapeutic potential in asthma and COPD. *Treat. Respir. Med.* **2005**, *4*, 85−94.
(21) Bendas, G. Inhibitors of membrane receptors involved with leukocyte extravasation. *Mini-Rev. Med. Chem.* **2005**, *5*, 575−584.
(22) Slee, D. H.; Romano, S.; Yu, J.; Nguyen, T. N.; John, J. K.; Raheja, N. K.; Axe, F. U.; Jones, T. K.; Ripka, W. C. Development of potent noncarbohydrate imidazole-based small molecule selectin inhibitors with anti-inflammatory activity. *J. Med. Chem.* **2001**, *44*, 2094−2107.
(23) Ohta, S. Y.; Inujima, Y.; Abe, M.; Uosaki, Y.; Sato, S.; Miki, I. Inhibition of P-selectin specific cell adhesion by a low molecular weight, noncarbohydrate compound, KF38789. *Inflammation Res.* **2001**, *50*, 544−551.
(24) Schön, M. P.; Krahn, T.; Schön, M.; Rodriguez, M.-L.; Antonicek, H.; Schultz, J. E.; Ludwig, R. J.; Thomas M.; Zollner, T. M.; Bischoff, E.; Bremm, K.-D.; Schramm, M.; Henninger, K.; Kaufmann, R.; Gollnick, H. P. M.; Parker, C. M.; Boehncke, W.-H. Efomycine M, a new specific inhibitor of selectin, impairs leukocyte adhesion and alleviates cutaneous inflammation. *Nature Med.* **2002**, *8*, 366−372.
(25) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H. H.; Keith, J. C., Jr.; Nickerson-Nutter, C.; Shilling, A.; Young-Sciame, R.; Wang, Q. Synthesis and biological evaluation of quinoline salicylic acids as P-selectin antagonists. *J. Med. Chem.* **2007**, *1*, 21−39.
(26) Compound 1 showed less than 10% bioavailability in mice.
(27) Sutherland, L. H.; Sloboda, A. E.; Child, R. G.; Poletto, J. F.; Powell, D. W. 2-Phenyl-4-quinoline carboxylic acids. U.S. Patent 1989/4847381, 1989.
(28) Mederski, W.; Osswald, M.; Dorsch, D.; Wilm, C.; Schmitger, C. J.; Christadler, M. Endothelin receptor antagonists. U.S. Patent 1998/5731321, 1998.
(29) (a) Hesson, D. P. Preparation of 2-phenyl-4-quinolinecarboxylates as antitumor agents. U.S. Patent 1987/4680299, 1987. (b) Ackerman, N. R.; Jaffee, B. D.; Loveless, S. E.; Neubauer, R. H. Preparation of 4-quinolinecarboxylic acid derivatives as immunosuppressive agents. Eur. Patent 1989/339485 A1, 1989.
(30) Kaila, N.; Debernardo, S. L.; Janz, K. M.; Camphausen, R. T.; Bedard, P. W.; Huang, A. Preparation of fused quinoline derivatives as selectin inhibitors. U.S. Pat. Appl. Publ. 2005101569 A1, 2005.
(31) (a) Cragoe, E. J.; Robb, C. M.; Bealor, M. D. The synthesis of 3-hydroxycinchoninic acid and certain of its derivatives. *J. Org. Chem.* **1953**, *18*, 552−560. (b) Cragoe, E. J.; Bealor, M. D.; Robb, C. M.; Ziegler, C.; Sprague, J. M. The synthesis of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid and certain of its derivatives. *J. Org. Chem.* **1953**, *18*, 561−569.
(32) (a) Sandmeyer, T. Isonitrosoacetanilides and their condensation to form isatin derivatives. *Helv. Chim. Acta* **1919**, *2*, 234−242. (b) Yang, K.; Campbell, B.; Birch, G.; Williams, V. E.; Lemieux, R. P. Induction of a ferroelectric S_C* liquid crystal phase by an atropisomeric dopant derived from 4,4′-dihydroxy-2,2′-dimethyl-6,6′-dinitrobiphenyl. *J. Am. Chem. Soc.* **1996**, *118*, 9557−9561. (c) Marvel, C. S.; Hiers, G. S. Isatin. *Org. Synth.* **1925**, *V*, 71−74.
(33) Cook, J. W.; Loudon, J. D.; McCloskey, P. The chemistry of the mitragyna genus. *J. Chem. Soc.* **1952**, 3904−3912.
(34) Huo, S. Highly efficient, general procedure for the preparation of alkylzinc reagents from unactivated alkyl bromides and chlorides. *Org. Lett.* **2003**, *5*, 423−425.
(35) Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. Synthesis and analogues of 1,3-dihydroxyacetone phosphate and glyceraldehyde 3-phosphate for use in studies of fructose-1,6-diphosphate aldolase. *J. Org. Chem.* **1988**, *53*, 3457−3465.
(36) Kaila, N.; Somers, W. S.; Thomas, B. E.; Janz, K.; Thakker, P.; DeBernardo, S.; Tam, S. Y.; Yang, R.; Moore, W.; Wrona, W.; Bedard, P. W.; Crommie, D.; Tsao, D.; Alvarez, J. C.; Keith, J.; Alvarez, J. C.; Ni, H.; Wagner, D. D.; Marchese, E.; Patton, J. T.; Magnani, J. L.; Camphausen, R. T. Quinic acid derivatives as sialyl Lewis^x-mimicking selectin inhibitors: Design, synthesis and crystal structure in complex with E-selectin. *J. Med. Chem.* **2005**, *48*, 4346−4357 and references therein.
(37) Compounds **67** and **69** were not taken forward because they displayed poor microsomal stability in rats ($t_{1/2}$ of 6 min). Compound **90** was not pursued due to very poor aqueous solubility. Compound **142** was not pursued due to stability issues under the Biacore assay conditions. The esters (**103**, **104**, and **105**) were not pursued because they generally have poor pharmacokinetic properties.
(38) Mayer, M.; Meyer, B. Characterization of ligand binding by saturation transfer difference NMR spectroscopy. *Angew. Chem., Int. Ed.* **1999**, *38*, 1784.
(39) Lepre, C. A.; Moore, J. M.; Peng, J. W. Theory and applications of NMR−based screening. *Pharm. Res. Chem. Rev.* **2004**, 3641−3675.
(40) Compound **79** was discarded due to very poor solubility in the Biacore and NMR assay.
(41) Ley, K.; Bullard, D. C.; Arbones, M. L.; Bosse, R.; Vestweber, D.; Tedder, T. F.; Beaudet, A. L. Sequential contribution of L- and P-selectin to leukocyte rolling in vivo. *J. Exp. Med.* **1995**, *181*, 669−675.
(42) Hicks, A. E. R.; Leppanen, A.; Cummings, R. D.; Mcever, R. P.; Hellewell, P. G.; Norman, K. E. Glycosulfopeptides modeled on P-selectin glycoprotein ligand 1 inhibit P-selectin-dependent leukocyte rolling in vivo. *FASEB J.* **2000**, *16*, 1461−1462.
(43) Somers, W. S.; Tang, J.; Shaw, G. D.; Camphausen, R. T. Insights into the molecular basis of leukocyte tethering and rolling revealed by structures of P- and E-selectin bound to sLe^x and PSGL-1. *Cell* **2000**, *103*, 467−479.
(44) Kumar, A.; Villani, M. P.; Patel, U. K.; Keith, J. C., Jr.; Schaub, R. G. Recombinant soluble form of PSGL-1 accelerates thrombolysis and prevents reocclusion in a porcine model. *Circulation* **1999**, *99*, 1363−1369.
(45) Khor, P. S.; Mccarthy, K.; Dupont, M.; Murray, K.; Timony, G. Pharmacokinetics, pharmacodynamics, allometry, and dose selection of rPSGL−Ig for phase I trial. *J. Pharmacol. Exp. Ther.* **2000**, *293*, 618−624.
(46) Kogan, T. P.; Dupre, B.; Bui, H.; McAbee, K. L.; Kassir, J. M.; Scott, I. L.; Hu, X.; Vanderslice, P.; Beck, P. J.; Dixon, R. A. F. Novel synthetic inhibitors of selectin-mediated cell adhesion: Synthesis of 1,6-bis[3-(3-carboxymethylphenyl)-4-(2-α-D-mannopyranosyloxy)phenyl]hexane (TBC1269). *J. Med. Chem.* **1998**, *41*, 1099−1111.
(47) Abraham, W. M.; Ahmed, A.; Sabater, J. R.; Lauredo, I. T.; Botvinnikova, Y.; Bjercke, R. J.; Hu, X.; Revelle, M. B.; Kogan, T. P.; Scott, I. L.; Dixon, R. A. F.; Yeh, E. T. H.; Beck, P. J. Selectin blockade prevents antigen-induced late bronchial responses and airway hyper-responsiveness in allergic sheep. *Am. J. Respir. Crit. Care Med.* **1999**, *159*, 1205−1214.
(48) Langer, R.; Wang, M.; Stepkowski, S. M.; Hancock, W. W.; Han, R.; Li, P.; Feng, L.; Kirken, R. A.; Berens, K. L.; Dupre, B.; Podder, H.; Dixon, R. A. F.; Kahan, B. D. Selectin inhibitor bimosiamose prolongs survival of kidney allografts by reduction in intragraft production of cytokines and chemokines. *J. Am. Soc. Nephrol.* **2004**, *15*, 2893−2901.

(49) Wang, K.; Zhou, Z.; Zhou, X.; Tarakji, K.; Topol, E. J.; Lincoff, A. M. Prevention of intimal hyperplasia with recombinant soluble P-selectin glycoprotein ligand-immunoglobulin in the porcine coronary artery balloon injury model. *J. Am. Coll. Cardiol*. **2001**, 577−82.
(50) Hayashi, S.; Watanabe, N.; Nakazawa, K.; Suzuki, J.; Tsushima, K.; Tamatani, T.; Sakamoto, S.; Isobe, M. Roles of P-selectin in inflammation, neointimal formation, and vascular remodeling in balloon-injured rat carotid arteries. *Circulation* **2000**, *102*, 1710−1717.
(51) Zhou, Z.; Penn, M. S.; Forudi, F.; Zhou, X.; Tarakji, K.; Topol, E. J.; Lincoff, M. A.; Wang, K. Administration of recombinant P-selectin glycoprotein ligand Fc fusion protein suppresses inflammation and neointimal formation in Zucker diabetic rat model. *Arterioscler., Thromb., Vasc. Biol.* **2002**, *22*, 1598−1603.
(52) Dong, Z. M.; Brown, A. A.; Wagner, D. D. Prominent role of P-selectin in the development of advanced atherosclerosis in Apo E-deficient mice. *Circulation* **2000**, *101*, 2290−2295.
(53) Bedard, P. W.; Clerin, V.; Sushkova, N.; Darby, A.; DeBernardo, S.; Eppihimer, M. J.; Harding, K.; Janz, K.; Kaila. N.; Keith, J. C.; Tavares, J.; Schaub, R. G.; Shaw, G. D. A novel P-selectin inhibitor, 31, demonstrates positive activity following oral administration in rodent models of vascular inflammation. Proceedings of the International Society of Thrombosis and Haemostasis Meeting, Sydney, Australia, August 6, 2005. Manuscript for publication in preparation.
(54) Clerin, V.; Resmini, C.; Darby, A.; Tavares, J.; Harding, K.; Wong, T.; Bedard, P.; Shaw, G.; Keith, J. C.; Kaila, N.; DeBernardo, S.; Janz, K.; Schaub, R. G. WAY-197697, a P-selectin antagonist, reduces atherosclerosis and intimal hyperplasia in animal models of vascular disease. Proceedings of the 77th American Heart Association Scientific Sessions 2004, New Orleans, LA, November 7−10, 2004. Manuscript for publication in preparation.
(55) Myers, D. D.; Rectenwald, J. E.; Bedard, P. W.; Kaila, N.; Shaw, G. D.; Schaub, R. G.; Farris, D. M.; Hawley, A. E.; Wrobleaski, S. K.; Henke, P. K.; Wakefield, T. W. Decreased venous thrombosis with an oral inhibitor of P selectin *J. Vasc. Surg*. **2005**, *42*, 329−336.
(56) Rewcastle, G. W.; Atwell, G. J.; Zhuang, L.; Baguley, B. C.; Denny, W. A. Potential antitumor agents. 61. Structure−activity relationships for in vivo colon 38 activity among disubstituted 9-oxo-9H-xanthene-4-acetic acids. *J. Med. Chem.* **1991**, *34*, 217−222.
(57) Lisowski, V.; Robba, M.; Rault, S. Efficient synthesis of novel 3-(Het)arylanthranilic acids via a Suzuki cross-coupling reaction of 7-iodoisatin with (Het)arylboronic acids in water. *J. Org. Chem.* **2000**, *65*, 4193−4194.
(58) Arndt, F. Diazomethane. *Org. Synth.* **1935**, *XV*, 3−5.
(59) Huo, S. Highly efficient, general procedure for the preparation of alkylzinc reagents from unactivated alkyl bromides and chlorides. *Org. Lett.* **2003**, *5*, 423−425.
(60) Cragoe, E. J., Jr.; Robb, C. M. 3-Hydroxyquinoline. *Org. Synth.* **1960**, *40*, 54−60.
(61) Thomas, A.; Jensen, T. A.; Liang, X.; Tanner, D.; Skjaerbaek, N. Rapid and efficient microwave-assisted synthesis of aryl aminobenzophenones using Pd-catalyzed amination. *J. Org. Chem.* **2004**, *69*, 4936−4947.
(62) Goetz, D. J.; Greif, D. M.; Ding, H.; Camphausen, R. T.; Howes, S.; Comess, K. M.; Snapp, K. R.; Kansas, G. S.; Luscinskas, F. W. Isolated P-selectin glycoprotein ligand-1 dynamic adhesion to P- and E-selectin. *J Cell Biol.* **1997**, *137*, 509−519.
(63) Sako, D.; Comess, K. M.; Barone, K. M.; Camphausen, R. T.; Cumming, D. A.; Shaw, G. D. A sulfated peptide segment at the amino terminus of PSGL-1 is critical for P-selectin binding. *Cell* **1995**, *83*, 323−331.
(64) Myszka D. G. Improving biosensor analysis. *J. Mol. Recognit.* **1999**, *12*, 279−284.

JM060631P