CoMFA, Synthesis, and Pharmacological Evaluation of (*E*)-3-(2-Carboxy-2-arylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acids: 3-[2-(3-Aminophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, a Potent Selective Glycine-Site NMDA Receptor Antagonist†

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(*E*)-3-(2-Carboxy-2-phenylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid, **1**, is a potent and selective antagonist of the glycine site of the *N*-methyl-D-aspartate (NMDA) receptor. Using 3D comparative molecular field analysis (CoMFA) to guide the synthetic effort, a series of aryl diacid analogues of **1** were synthesized to optimize in vivo potency, duration of action, and binding activity. It was found that the incorporation of a substituted aromatic with an electron withdrawing group or a heterocyclic group at the 2-position of the 3-propenyl moiety of **1** gave compounds with better affinity and potency in the murine stroke model. Ultimately this led to the discovery of 3-[2-(3-aminophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic acid, **19**, as a new potent selective glycine-site NMDA receptor antagonist.

Introduction

Overactivation of the *N*-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor in the brain and central nervous system, by elevated levels of glutamic acid as a result of a neurodegenerative event such as cerebral ischemia or neurotrauma, allows excess calcium to enter the neuronal cell.[1] This calcium influx activates endogenous, calcium-dependent, degradative enzymes that are believed to destroy the neuron cell before the damaged cell can mutate. Glutamate antagonists have been shown to disrupt this chain of events at the surface of the cell at the glycine NMDA site.[2]

Glycine, an obligatory coagonist for the NMDA receptor,[3] activates ion channels at a strychnine-insensitive binding site[4] distinct from that utilized by glutamate.[5] It has been demonstrated that glycine antagonists can mediate NMDA receptor response in vitro and in vivo[6] and are noncompetitive antagonists of glutamate. Intervention at this site could offer a potential mechanistic advantage, since a glycine antagonist would not have to compete with the ischemia-induced elevated levels of glutamate. Therefore, a glycine-site NMDA receptor antagonist might have an application for neuroprotection in stroke and head trauma.[7]

Compound **1** (Figure 1) is a potent glycine antagonist with affinity for the glycine-site NMDA receptor (IC_{50} vs [^{3}H]glycine of 11 nM) and is centrally active as demonstrated by anticonvulsant activity (ED_{50} vs audiogenic seizures of 12 mg/kg intraperitoneally (ip) and 29 mg/kg intraveneously (iv) vs maximal electroshock in the rat).[8] A chemical optimization program was initiated on the basis of 3D comparative molecular field analysis (CoMFA) of **1** to improve the pharmacological properties.

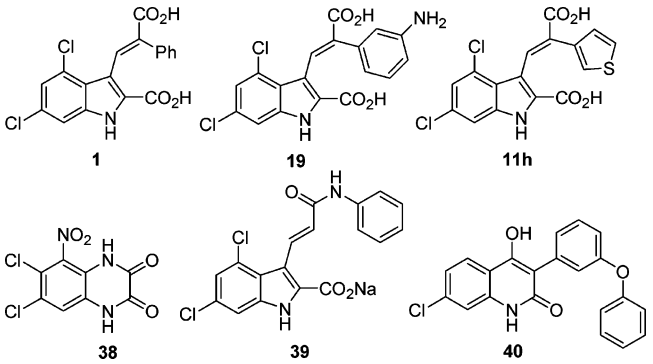

Figure 1. Potent NMDA inhibitors.

CoMFA of Inhibitor 1

CoMFA is a well accepted three-dimensional quantitative structure−activity relationship (3D-QSAR) method for providing insight into the possible conformation of a molecule close to or in its active form. We have used CoMFA to establish a 3D structure that could represent the active conformation of **1** on the basis of a set of analogues.

CoMFA studies were performed on approximately 300 compounds related to **1** to provide a series of target molecules for synthesis and biological evaluation. All structures shown in Table 1 were constructed in SYBYL 6.6.[9] Compound **1** was subjected to conformational analysis, and the lowest energy conformation, calculated using the Tripos 5.2 force field as available within SYBYL, was used as a template to construct the other structures listed in Table 1. The ionizable groups in each compound were kept in the neutral state. All structureswere then subjected to optimization using the AM1

† Dedicated to Prof. John "Jack" Martin on the occasion of his return to the classroom from retirement.

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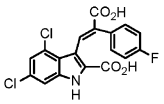
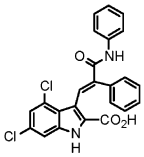
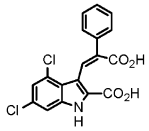
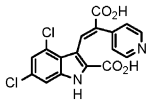
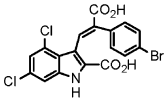
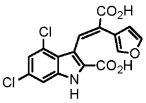
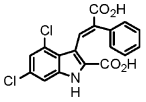
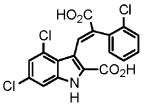
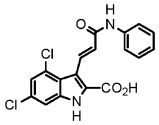
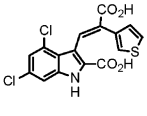
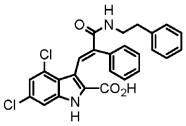
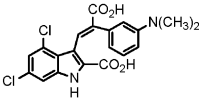
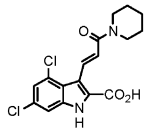
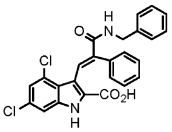
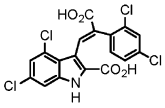
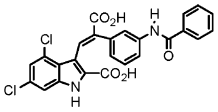
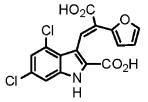
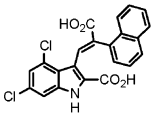
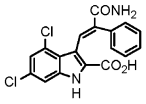
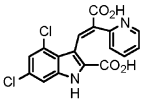
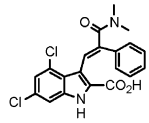
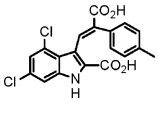
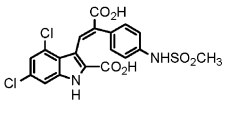
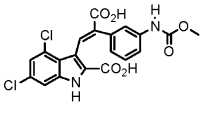
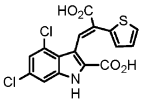
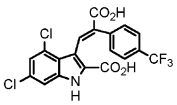
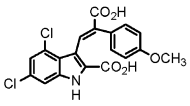
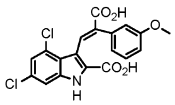
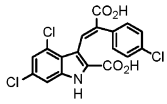
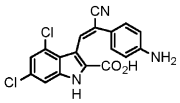
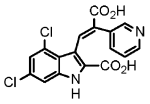
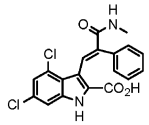
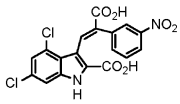
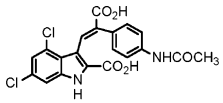
Table 1. Compounds Used in the CoMFA

No	structure	IC50(μM)	No	structure	IC50(μM)	No	structure	IC50(μM)	No	structure	IC50(μM)
17a		0.0355	13a		0.015			0.157	**22d**		0.151
17c		0.029	11e		0.021	1		0.011	17h		0.212
		0.015	11h		0.014	13f		0.224	21e		0.225
		0.038	13b		0.031	11c		0.116	21b		0.512
11d		0.022	**11b**		0.145	13d		0.02	22b		1.025
13e		0.068	17e		0.105	21d		0.167	21c		0.114
11g		0.009	**17f**		0.089	11i		0.136	32c		0.117
11f		0.065	26a		4.664	**22c**		0.126			
13c		0.05	17g		0.021	21a		0.462			

Hamiltonian in MOPAC 4.0 [10] (as supplied within SYBYL). The structures were then overlaid using the indole group and the adjacent carboxylic group as the template.

A region was constructed around the parts of the structure showing variation only as shown in Figure 2. The dimensions of the CoMFA[11] region were 23 × 11 × 20 Å with a 1 Å spacing along the three axes. A 2 kcal minimum σ value was used, and correspondingly 8401 out of possibly 10121 points were dropped from the CoMFA. A proton and an sp^3 carbon were used as probes in the CoMFA to evaluate the electrostatic and steric fields, respectively. A cutoff of 30 kcal and greater in the steric field was used to drop the electrostatic field computation at the corresponding CoMFA grid points. Compounds in bold and underlined in Table 1 were not used in the learning set of the CoMFA and were only used as a prediction set. The fitted vs actual pIC50 values are shown in Figure 3 together with the statistics from the PLS analysis of the 28 compounds in the learning set.

The steric contribution amounted to 48.5%. Contours of (std dev) × (coeff) (hereafter referred to as coefficients), for the steric and electrostatic fields are represented in Figure 2. The positive (0.003) steric field coefficients are shown in green, the negative coefficients (−0.003) in red, and the electrostatic field coefficients are shown in yellow (0.009) and cyan (−0.009), respectively.

The overlap of the positive steric coefficient contour with the positive electrostatic contour suggests a positively charged or less negatively charged substitution pattern in that region. The negative coefficient contours clearly delineate a pocket in the NMDA receptor into which the compounds fit with the phenyl group of compound **1** sitting in a pocket that conservatively prefers a relatively less negatively charged substituent. As a result of the CoMFA studies a chemical optimization program was initiated and directed toward modification or replacement of the phenyl group at the 2-position of the 3-propenyl moiety of **1**.

Chemistry

Compound **1** was first synthesized in seven steps from 3-iodo-2-(ethoxycarbonyl)-4,6-dichloroindole[12] and 2-phenyl-3-(tributylstannyl)acrylic acid methyl ester using a Stille coupling strategy (Scheme 1). For the task of chemical optimization a more efficient route was neces-

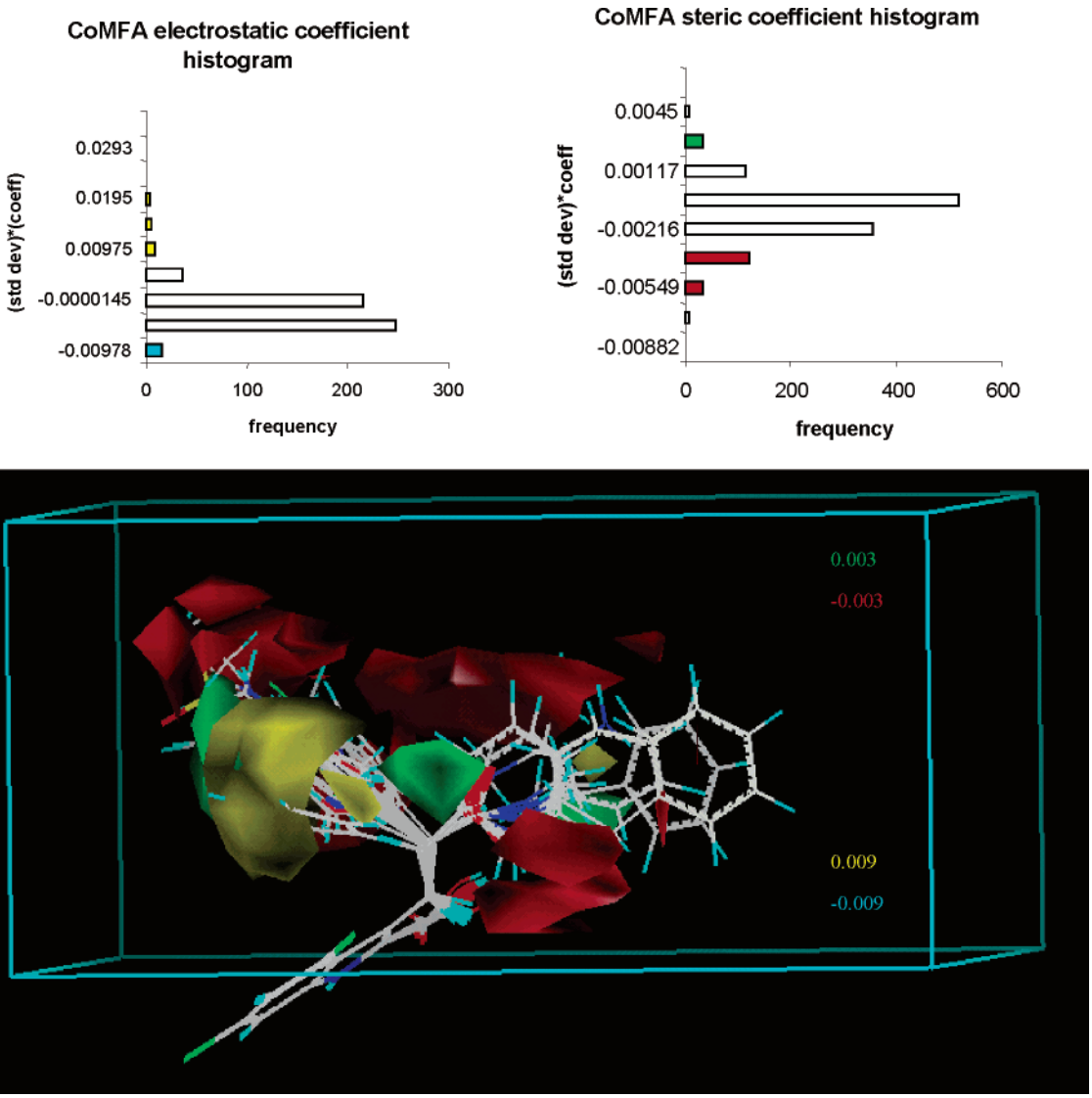
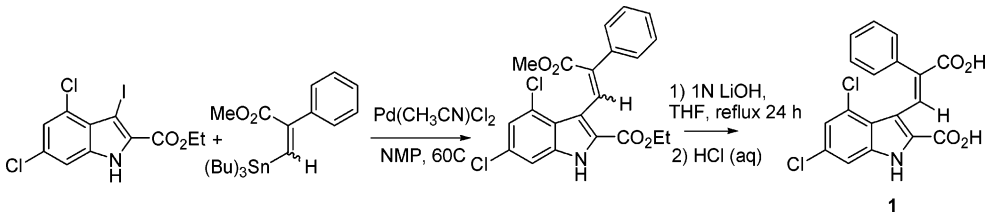


Figure 2. Compounds in Table 1 overlaid after optimzation and shown together with the steric and electrostatic coefficients in the CoMFA region. Also shown are the steric and electrostatic coefficient histograms.

Scheme 1



sary to identify and prepare a common intermediate that could accommodate the regiospecific introduction of a variety of substituted aryl groups and heteroaryls at the 2-position of the 3-propenyl moiety of **1**, preferably at a late stage in the synthetic sequence.

Several different synthetic stategies were investigated to prepare a number of structurally diverse analogues of **1**. All of the synthetic routes described have advantages and disadvantages depending on the desired functionality incorporated.

Suzuki−Miyaura Reaction. The in situ palladium(0)-catalyzed Suzuki−Miyaura reaction is an efficient method for the cross-coupling of aryl boranes with vinyl bromides.[13] The reaction of the (*Z*)-indole vinyl bromide **8*Z*** with the appropriate arylboronic acid provides easy access to analogues of **1**. An attractive feature of this approach is that a variety of arylboronic acids are commercially available, and those of interest which are not can easily be prepared from the corresponding aryllithium (halogen metal exchange) species by treatment with a trialkoxyborane.

Vinyl bromide **8*Z*** was prepared on a multigram scale utilizing the synthetic sequence shown in Scheme 2. Formylation of 4,6-dichloro-*H*-indole-2-carboxylic acid ethyl ester **5**[14] affords aldehyde **6**. Protection of the indole nitrogen with *p*-toluenesulfonyl chloride and treatment with bromophosphonoacetate **4** (prepared fresh from the corresponding *tert*-butyl diethoxyphospho-

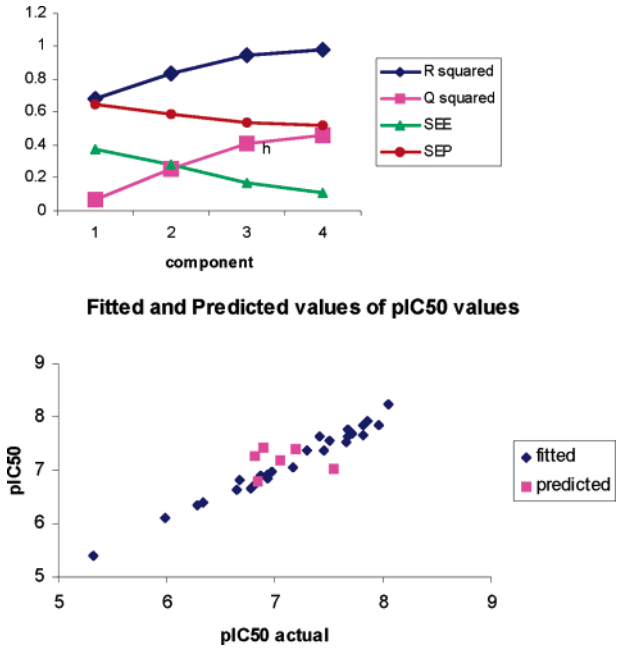
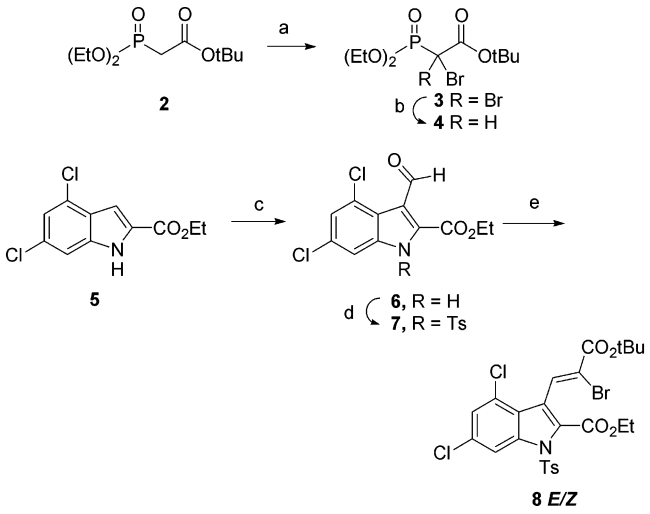


Figure 3. Statistic describing the PLS method and the fitted and predicted versus actual pIC_{50} values from the CoMFA.

Scheme 2[a]



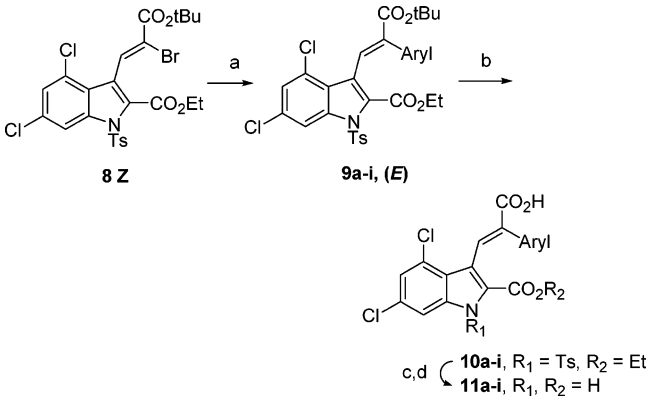
[a] Reactions and conditions: (a) Br_2, aq. NaOH, i-PrOH; (b) $SnCl_2$, H_2O, *t*-BuOH; (c) $POCl_3$, DMF; (d) pTsCl, anhyd. K_2CO_3; (e) **4**, LiHMDS, THF.

noacetate[15] via dibromination with NaOBr and monodebromination with $SnCl_2$) under Horner–Emmons conditions provided the indole vinyl bromide **8** as an *E*/*Z* mixture. Fractional recrystallization (pentane/Et_2O) gave the desired vinyl bromide **8*Z*** in 65% yield.

The stereochemistry of the vinyl bromide was assigned using proton NMR. The vinyl proton of vinyl bromide **8*Z*** is deshielded and gives a singlet at 8.2 ppm, while the proton of **8*E*** is observed as a singlet at 7.5 ppm. The *tert*-butyl ester protons of vinyl bromide **8*Z*** give a singlet at 1.6 ppm, while the corresponding protons of **8*E*** are shielded by the indole ring, shifting their signal upfield to 1.0 ppm.

Vinyl bromide **8*Z*** was coupled with various commercially available arylboronic acids[16] using one of two methods. Method A involves the use of $(Ph_3P)_4Pd/K_2CO_3$ [17] as the catalyst in toluene at 90–100 °C, while method B involves the use of tris(dibenzylideneacetone)

Scheme 3[a]



[a] Reactions and conditions: (a) aryl-$B(OH)_2$, anhyd. K_2CO_3, $(Ph_3P)_4Pd$, tol. or $Pd_2(dba)_3$, (2-furyl)$_3$Pd, THF; (b) TFA or HCO_2H; (c) LiOH, THF, H_2O; (d) $KHSO_4$. Structures: aryl; **a** = phenyl; **b** = naphthalen-1-yl; **c** = 2,4-dichlorophenyl; **d** = 2-furyl; **e** = 3-furyl; **f** = 4-chlorophenyl; **g** = 2-thienyl; **h** = 3-thienyl; **i** = 4-methoxyphenyl.

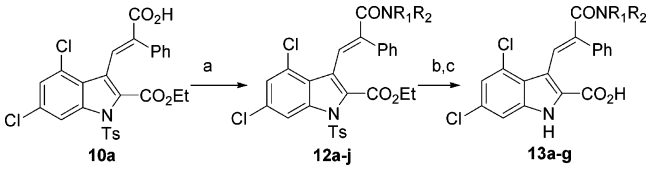
dipalladium(0) [$Pd_2(dba)_3$]/tris(2-furyl)phosphine/K_2CO_3 [18] in tetrahydrofuran (THF) at 55–60 °C (Scheme 3). Method A was used for the coupling of the phenyl-, 1-naphthyl-, 2,4-dichlorophenyl-, 2-furyl, 3-furyl, and (*p*-chlorophenyl)boronic acids, which gave products **9a–f** in 51–71% yield. Method B was employed for the coupling of the electron-rich 2-thienyl, 3-thienyl, and (*p*-methoxyphenyl)boronic acids to afford the coupled products **9g–i** in 77, 49, and 46% yields, respectively. The coupled products **9a–i** possess only the desired *E*-stereochemistry, simplifying purification and characterization of the products and their derivatives. The Suzuki coupling using method A required reaction times of 4 h to overnight, while couplings using method B required reaction times of 6–9 days.

Attempted coupling of (*p*-methoxyphenyl)boronic acid to vinyl bromide **8*Z***, using [1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) acetate as a catalyst,[19] provided a 5:1 mixture of **9i** and unreacted vinyl bromide **8*Z*** after 10 days in THF at 55–60 °C. The use of $Pd_2(dba)_3$ as the catalyst in the *absence* of any phosphine ligands, a procedure reported to greatly increase the rate and efficiency of coupling,[20] did not result in any apparent coupling after 24 h at 55–60 °C.

Products **9a–i** were only slightly more polar than the vinyl bromide **8*Z***, making the purification of the crude diester difficult. Deprotection of the *tert*-butyl esters of these crude intermediates with either TFA or HCO_2H afforded the monoacids **10a–i**, which were highly crystalline. As a result, they were easily separated from the (*Z*)-bromo acid and other contaminants, such as dibenzylideneacetone (method B), by fractional recrystallization or by trituration with pentane containing a small amount of Et_2O. Hydrolysis of **10a–i** with LiOH in THF/H_2O provided the desired diacids **11a–i**.

The absence of a significant upfield shift of either the *tert*-butyl ester or the vinyl protons in the proton NMRspectra of **9–11** indicated that isomerization of the *E*-acids to the *Z*-acids did not occur in either the coupling reaction or the subsequent deprotection steps. Notably, the proton NMR spectrum of the 1-naphthyl ester **9b** suggested that the naphthyl ring is situated directly above the 2-carboethoxy group, as the methylene protons are highly shielded and differentiated,

Scheme 4[a]



[a] Reactions and conditions: (a) HNR_1R_2, EDC, HOBt; (b) LiOH, THF, H_2O; (c) $KHSO_4$. Structures: **a**, $R_1 = H$, $R_2 = Ph$; **b**, $R_1 = H$, $R_2 = Bn$; **c**, $R_1 = H$, $R_2 = Me$; **d**, R_1, $R_2 = H$; **e**, R_1, $R_2 = Me$; **f**, $R_1 = H$, $R_2 = CH_2CH_2Ph$; **g**, R_1, $R_2 = -(CH_2CH_2)_2O$; **h**, $R_1 = H$, $R_2 =$ OBn; **i**, $R_1 = H$, $R_2 = OH$; **j**, $R_1 =$ tBOC, $R_2 =$ OTBDMS.

absorbing at 3.63 and 2.79 ppm. This conformation was indeed confirmed in the molecular modeling global minimization of **9b** in preparation for a CoMFA analysis of diacids **11**.

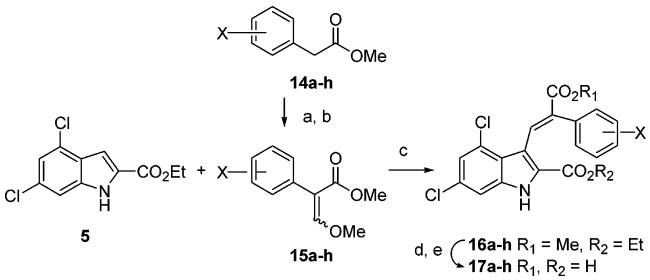
A key feature in this synthetic route was the introduction of a *tert*-butyl ester at the vinyl position, distinguishing that ester from the ethyl ester at the 2-position on the indole ring. The difference in reactivity of these esters allowed for selective hydrolysis of the *tert*-butyl ester **9a** with TFA, providing the monoacid **10a**, which upon further functionalization gave a variety of novel amide derivatives **13a**−**g** (Scheme 4).

Intermediate **10a** was reacted with various amines by activating the carboxylic acid with EDC/HOBT to afford, after hydrolysis, the amide acid analogues **13a**−**g**. Synthesis of the hydroxamic acid analogue **13i** was unsuccessful. The initial reaction to couple **10a** with *O*-benzylhydroxylamine to give the intermediate *O*-benzylamide **12h** was successful. However, attempted debenzylation using either HBr/AcOH or PdO/cyclohexene resulted in overreduction to the primary amide **12d**. An alternative route coupling *N*-*t*-Boc-*O*-TBDMS hydroxylamine[21] with the acid chloride of **10a** (prepared from the reaction of the carboxylic acid with oxalyl chloride) gave the *N*-*t*-Boc-*O*-TBDMS amide **12j**. Deprotection of this compound with TFA/CsF gave the protected hydroxamic acid **12i**. However, removal of the *p*-tosyl group and the ethyl ester using either LiOH/THF/H_2O or K_2CO_3/THF/H_2O resulted in destruction of the hydroxamic acid moiety as shown by a negative $FeCl_3$ test. Further attempts were not made to synthesize **13i**.[22] Additional amide analogues of **13** were not synthesized due to the inactivity of compounds **13a**−**g** in the DBA/2J audiogenic seizure model. This lack of activity was attributed to poor CNS penetration.

Nuclear Overhauser effect (NOE) studies on amide ester **12g** confirmed the stereochemical assignments, since *strong* NOEs were observed between the vinyl proton and the proximal morpholine protons, while only a *weak* NOE was observed between the vinyl proton and the phenyl protons.

Lewis Acid-Catalyzed Enol Ether Condensation. The utility of the Suzuki−Miyaura coupling reaction was limited by the substituent on the arylboronic acid aromatic ring. Arylboronic acids possessing electron-withdrawing substituents on the aromatic ring either gave poor yields or no reaction with the starting material being recovered. The Lewis acid-catalyzed (trimethylsilyltriflate) condensation of indole ester **5** via a preformed enol ether **15a**−**h** offered an alternative method for preparing target compounds **17a**−**h** (Scheme 5).

Scheme 5[a]



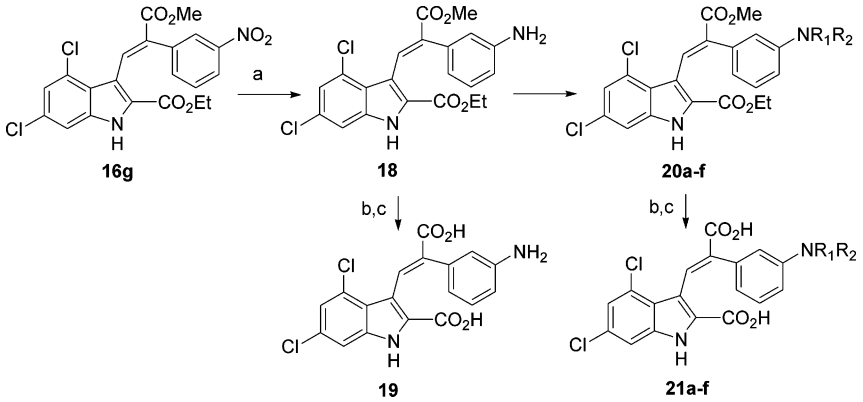
[a] Reactions and conditions: (a) NaH/MeOH, THF, HCO_2Et; (b) MeI, DMF; (c) TMSOTf, CH_2Cl_2; (d) LiOH, THF, H_2O (e) $KHSO_4$. Structures: X = **a**, *p*-F; **b**, *p*-Cl; **c**, *p*-Br; **d**, *p*-I; **e**, *p*- Me; **f**, *p*-CF_3; **g**, *m*-NO_2; **h**, *o*-Cl.

Enol ether **15a** was prepared in a two-step, one-pot reaction starting with methyl *p*-fluorophenylacetate (**14a**), NaH, and HCO_2Me in THF. A drop of MeOH was added to initiate the reaction and impede the occurrence of a sudden exotherm. Quenching with MeI in dimethylformamide (DMF) provided the crude enol ether **15a** in 82% yield, which was subsequently condensed with the indole ester **5** in the presence of a Lewis acid. Several acids ($BF_3{\cdot}OEt_2$, Me_3OBF_4, and $TiCl_4$) were evaluated for the condensation reaction. TMSOTf provided the best yield and cleanest conversion to the desired product. An equivalent amount of Lewis acid was necessary for the reaction to occur since the formation of MeOH during the reaction consumes the catalyst. Typically the enol ethers were used in the coupling step without further purification due their instability to silica gel. TMSOTf-promoted coupling between the indole **5** and enol ether **15a** gave the desired diester **16a** in 53% as a 3:2 mixture of *E*/*Z* isomers. Hydrolysis of **16a** using aqueous NaOH solution at 95 °C for 16 h afforded the diacid following acid workup. Crystallization gave **17a** in 71% yield as the desired *E* isomer.

The *p*-chlorophenyl, *p*-bromophenyl, *p*-iodophenyl, *p*-tolyl, *p*-trifluoromethylphenyl, *m*-nitrophenyl, and *o*-chlorophenyl analogues, compounds **17b**−**h**, respectively, were prepared in a fashion similar to **17a**, utilizing the corresponding phenylacetic esters **14b**−**h**. All were obtained as *E*/*Z* mixtures. Saponification and recrystallization of the diacids afforded the desired *E* isomers, as identified by the characteristic location of the vinyl proton at ∼8.1 ppm in the proton NMR spectra. The application of this procedure appears to be limited to enol ethers having either electron-withdrawing or weakly electron-donating aryl groups, since neither the *m*- and *p*-methoxyphenyl- nor the 2- or 3-thienyl-substituted enol ethers afforded any of the desired coupled products.

m-Aminophenyl analogue **19** was synthesized from *m*-nitrophenyl diester **16g** (Scheme 6). Initial attempts to reduce the nitro group using Fe(0) gave poor yields and a mixtue of byproducts. Ultimately $SnCl_2$ was employed to give the desired *m*-aminophenyl diester **18** in 92% yield. The caveat in using this method was the difficult removal of the tin salts formed during the workup. Conversion of diester **18** to diacid **19** required rigorous hydrolysis conditions. Following treatment with LiOH, the aqueous layer was washed with EtOAc and acidified to pH 4 with 0.5 M $NaHSO_4$ solution. The

Scheme 6[a]



[a] Reactions and conditions: (a) $SnCl_2$, H_2O, i-PrOH; (b) LiOH, THF, H_2O; (c) $KHSO_4$. Structures: **a**, R_1 = H, R_2 = COMe; **b**, R_1 = H, R_2 = COPh; **c**, R_1 = H, R_2 = CO_2Me; **d**, R_1 = H, R_2 = SO_2Me; **e**, R_1, R_2 = Me; **f**, R_1 = H, R_2 = Me.

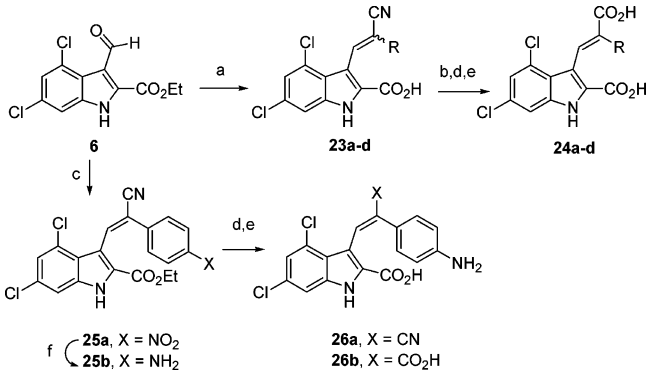
resulting precipitate was extracted with EtOAc. Removal of the solvent under reduced pressure afforded the crude product that was purified by recrystallization. Although several solvent systems such as EtOAc, EtOAc/hexane, acetone, and CH_3CN/H_2O were examined, none were effective in affording pure product. A two-step sequence, involving an initial crystallization from EtOAc followed by precipitation from MeOH with H_2O, gave pure **19** after drying under a stream of nitrogen, first at room temperature and then in vacuo at 80 °C.

m-Acylaminophenyl diacids **21a**−**d** were prepared by treatment of **18** with the corresponding acid chloride and Et_3N followed by saponification of the crude diesters **20a**−**d**. The resulting diacids were then purified by recrystallization. The *m*-dimethylamino analogue **21e** was prepared by reductive amination of the *m*-amino group.[23] Treatment of the *m*-aminophenyl diester **18** with paraformaldehyde and $NaBH_3CN$ in HOAc provided the desired *m*-(dimethylamino)phenyl diester **20e**. Saponification of the crude diester with LiOH followed by workup gave the desired diacid **21e**. A small amount of a methylated indole material, observed in the crude diester product, was removed by recrystallization of the diacid from EtOAc. The *m*-(methylamino)phenyl analogue **21f** was prepared by formylation of the *m*-aminophenyl diester **18** with HCO_2Et followed by selective reduction with $H_3B{\cdot}SMe_3$. Saponification of the resulting diester **20f** with LiOH, followed by workup, gave the desired diacid.

Knoevenagel Reaction. Utilization of the enol ether method was not applicable to the synthesis of analogues with substituted aromatics containing electron-donating groups. Therefore, the classical Knoevenagel condensation reaction[24] was explored as an alternative method to prepare analogues of this type. Attempts to condense aldehyde **6** with prospective arylacetic esters failed; however, when the appropriate arylacetonitrile **22a**−**d** was used, the corresponding arylpropenenitriles **23a**−**d** were generated, providing an easy entry into a limited series of analogues **24a**−**d** (Scheme 7).

A detailed account of the synthesis of analogues of **1** via this route has been reported.[25] A limitation of this method is that in most cases the hydrolysis of the arylpropenenitriles proceeds only to the respective amides, which will not hydrolyze further, even under more rigorous conditions, to the desired carboxylic acids. Only in the case of the substituted pyridine analogues

Scheme 7[a]



[a] Reactions and conditions: (a) R-CH_2CN, **22a**−**d**; (b) H_2SO_4, HOAc; (c) $NO_2C_6H_4CH_2CN$; (d) 6N NaOH; (e) $KHSO_4$; (f) $SnCl_2$. Structures: **22a**, R = Ph; **22b**, R = 2-pyridyl; **22c**, R = 3-pyridyl; **22d,** R = 4-pyridyl.

23b−**d** and the *p*-aminophenyl analogue **25b** were the corresponding nitriles successfully hydrolyzed to the desired diacids **24b**−**d** and **26b**.

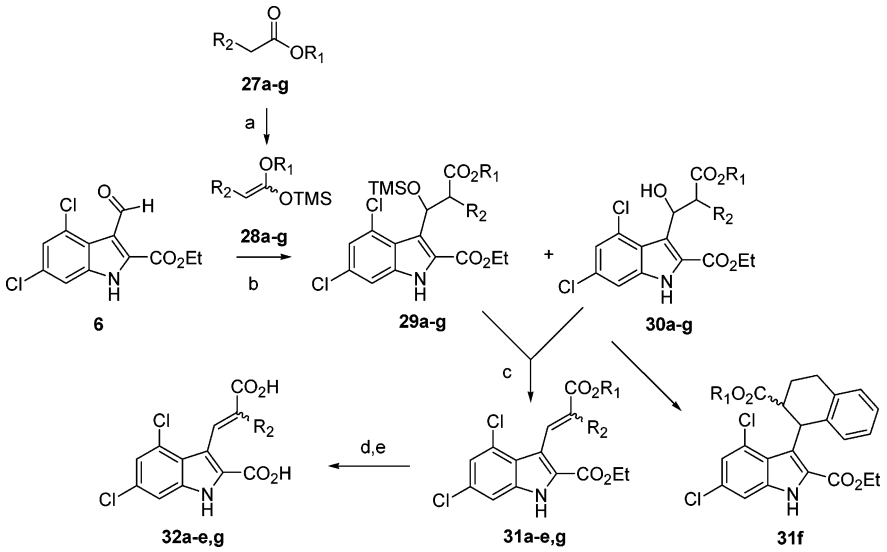
Mukaiyama Reaction. Although the condensation of *N*-tosyl aldehyde **7** with phosphonate **4** gave vinyl bromides **8** in good yield under Horner−Emmons conditions, the condensation of **7** with ethyl (diethylphosphono)phenylacetate was unsuccessful. Therefore, to prepare analogues of **1** which incorporate an arylacetic ester containing a relatively inactivated methylene group, an alternative coupling method using the Lewis acid-catalyzed aldol reaction of aldehyde **6** with various ketene silyl acetals such as **28**, also known as the Mukaiyama reaction[26] (Scheme 8), was explored. The success of the Mukaiyama reaction would rely on the transfer of the silyl group to the oxygen of the aldol to drive the reaction to completion.

Condensation of 1-methoxy-1-(trimethylsiloxy)-2-phenylethylene (**28a**)[27] with aldehyde **6** in the presence of $(Ph_3P{-}O{-}Ph_3P)^{2+}{\cdot}2TfO^-$ [28] at −78 to 0 °C gave 54% of *erythro*/*threo* aldols **30a** and 12% of the corresponding TMS ethers **29a**.

While 1-methoxy-1-(trimethylsiloxy)-2-(2-pyridyl)ethylene (**28b**) gave only the TMS ether **29b**, the ketene silyl acetal of methyl (*m*-phenoxyphenyl)acetate (**28d**) gave mostly the dehydrated product **31d** directly.

The aldol products proved to be versatile intermediates. Treatment with *p*-TsOH in refluxing toluene results in dehydration to the *E*/*Z* unsaturated esters in

Scheme 8[a]



[a] Reactions and conditions: (a) TMSOTf, Et_3N; (b) $Ph_3P{-}O{-}PPh_3^{2+}{\cdot}2TfO^-$; (c) pTsOH or Tf_2O; (d) LiOH, THF, H_2O; (e) $KHSO_4$. Structures: **a**; R_1 = Me, R_2 = Ph; **b**, R_1 = Et, R_2 = 2-pyridyl; **c**, R_1 = Me, R_2 = 3-methoxyphenyl; **d**, R_1 = Me, R_2 = 3-phenoxyphenyl; **e**, R_1 = Me, R_2 = Bn; **f**, R_1 = Me, R_2 = phenethyl; **g**, R_1 = Me, R_2 = cyclohexyl.

high yield. However, treatment of the silylated 2-pyridyl aldols **29b** with TFA at 25−45 °C gave *exclusively* ethyl 2-pyridylacetate and aldehyde **6** from a retro-aldol condensation. To avoid the retro-aldol and obtain the unsaturated ester **31b** *directly*, the silylated 2-pyridyl aldol **29b** was treated with Tf_2O at 0−25 °C *in the absence of added base*. The triflate, generated in situ, is apparently unstable and undergoes base-catalyzed elimination to the olefin. Running the reaction in the presence of proton sponge [1,8-bis(dimethylamino)-naphthalene] gave a complex mixture of products. The retro-aldol was not completely suppressed, but a ∼4.5:1 ratio of unsaturated esters **31b**/retro-aldol products were obtained. Saponification of ester **31b** provided pure *E* diacid **32b**; however, upon drying at 125 °C, the diacid isomerized to a 6:1 *E*/*Z* mixture. The desired *E* isomers of diacids **32c,d** were obtained exclusively after crystallization upon saponification of the intermediate *E*/*Z* diesters **31c,d**.

The preparation of analogues with the proximal phenyl ring replaced by benzyl, phenethyl, and cyclohexyl residues was also possible using the Mukaiyama route. Treatment of intermediates **29e,g** with *p*-TsOH in refluxing toluene resulted in dehydration to the novel unsaturated esters **31e** and **31g** in high yield. When (1-methoxy-3-phenyl-1-propenyloxy)trimethylsilane (**28e**) was condensed with aldehyde **6** under similar conditions and the mixture allowed to warm to room temperature with stirring over 16 h, neither the aldol nor the TMS ether **29e/30e** was observed due to in situ dehydration, possibly induced by excess Lewis acid during the extended reaction time. As a result, the desired unsaturated diester **31e** was isolated *directly* in moderate yield and was found to consist only of the *Z* isomer.

Assignment of olefin geometry in **31e** is based on NOE effects and vicinal proton−carbon coupling constants involving the olefinic proton, specifically a strong NOE interaction (ca. 20%) with the benzylic methylene protons, a large *anti*-coupling (ca. 13 Hz) to the ester carbonyl carbon, and a smaller *syn*-coupling (ca. 6.5 Hz) to the benzylic methylene carbon. Base hydrolysis of the unsaturated benzyl diester **31e** gave benzyl diacid analogue **32e** exclusively as the *Z* isomer, also determined by NOE studies. Likewise, in the analogous preparation of cyclohexyl diester **31g** and subsequent hydrolysis to diacid **32g**, only the respective *Z* isomers were isolated. In contrast, the adduct obtained from condensation of (1-methoxy-4-phenyl-1-butenyloxy)trimethylsilane (**28f**) with **6** under the same conditions gave analytical data consistent with structure **31f** (ca. 1:1 diastereomeric mixture), resulting from cyclization via intramolecular Friedel−Crafts alkylation.

Synthesis of the Saturated Analogue, *S*-3-(2-Carboxy-2-phenylethyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid (36)

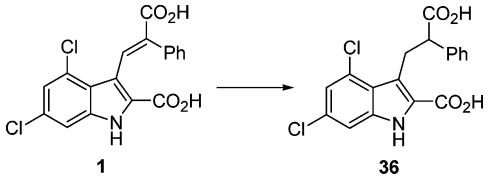
The CoMFA analysis showed that a low-energy conformer of the *S*-enantiomer of 3-(2-carboxy-2-phenylethyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid (**36**) overlapped very well with the lowest energy conformer of receptor-docked **1** (Figure 4). To test the validity of these calculations, compound **36** was synthesized, in its racemic form, along with several related alkyl diacid analogues and evaluated for NMDA receptor antagonist activity (Scheme 9).

The most obvious synthetic route to dihydro analogue **36** is the direct hydrogenation of **1**. Unfortunately, hydrogenation of **1** using H_2 at 60 psi with 10% Pd/C resulted in dechlorination, making it necessary to develop an alternate synthetic route. This was accomplished starting with *N*-tosyl aldehyde **7**. Protection of the indole nitrogen was necessary prior to reduction of the aldehyde to the alcohol. The aldehyde was reduced with $NaBH_4$ to give the alcohol **33**, which was then treated with $SOCl_2$ in refluxing toluene to afford the corresponding chloride **34**. Chloride **34** was converted with NaI to the iodide, which was reacted in situ with the anion of ethyl phenylacetate. The resulting dihydro diester, **35**, was hydrolyzed to afford the dihydro diacid **36** in moderate to good yield (Scheme 10).

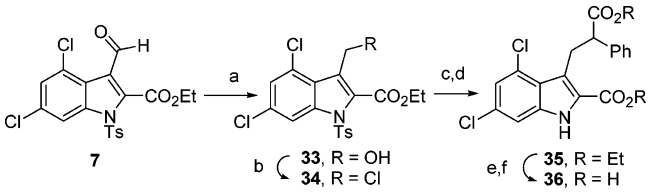
The Mukaiyama aldol route was also explored for the preparation of compound **36**. Treatment of the aldol

Figure 4. Overlay of compound **1**, with compound **36** in which the unsaturation has been removed.

Scheme 9

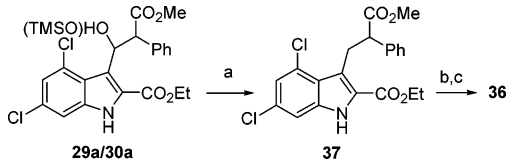


Scheme 10[a]



[a] Reactions and conditions: (a) $NaBH_4$; (b) $SOCl_2$; (c) NaI; (d) $PhCH_2CO_2Et$, NaH; (e) KOH; (f) HCl.

Scheme 11[a]



[a] Reactions and conditions: (a)TFA, Et_3SiH; (b) LiOH, THF, H_2O; (c) $KHSO_4$.

products, **29a/30a**, with TFA/Et_3SiH at room temperature gave only dihydro ester **37** without any trace of unsaturated ester **31a** resulting from dehydration (Scheme 11). $SnCl_4$/Et_3SiH was also effective, but less convenient, in reducing the aldol products. Saponification of dihydro ester **37**, followed by crystallization from cyclohexane/EtOAc, gave dihydro diacid **36** in good yield.

Pharmacology

Compounds were advanced from the binding assay to the in vivo anticonvulsant tests, the in vitro (inhibition of cGMP accumulation stimulated by NMDA in rat cerebellar slices) and in vivo (inhibition of harmaline-induced cGMP elevation in the cerebellum) biochemical functional assays in parallel. The number of compounds that have been evaluated through all the tests, including the stroke model, did not permit correlation of stroke results with any *single* test result, nor is it currently known what combination of in vivo and in vitro tests best correlate with activity in the stroke model. Thus, it would appear that good to excellent activity in most of the critical path tests and models is needed to identify those compounds which will exhibit significant neuroprotective results in the stroke model (see, for example, **38** vs **19**).

In Vitro Activity. The in vitro pharmacology described below reflects the critical discovery path used for evaluating the glycine site antagonists synthesized. The two main criteria for compound selection were the binding of the inhibitor to the NMDA receptor complex and functional assays to assess in vitro "efficacy". These two areas are outlined to demonstrate the primary activities measured.

The binding assays measured the affinity of the inhibitor and the benchmark/reference compounds for the glycine site on the NMDA receptor. The functional assays demonstrated NMDA antagonism in vitro and protection of the neuronal cell cultures from anoxia.

Compound **19** was found to be a potent antagonist (K_i = 24 nM) of [^{3}H]glycine binding to its recognition site on the NMDA receptor complex of rat brain. Activity resides exclusively with the *E* isomer of **19**. The *Z* isomer has been prepared and evaluated in key critical path assays as well as in in vitro assays predictive of side effect liability. The K_i value for the *Z* isomer in the [^{3}H]glycine binding assay was 553 nM. Values for **19** and reference compounds (Figure 1) are shown in Table 2.

Several biochemical methods confirmed **19** as a functional antagonist at the glycine site. For example, in a cerebellar slice preparation, NMDA elicits a concentration-dependent increase in the content of the second messenger substance cGMP. Compound **19** completely inhibited this response with an IC_{50} of 364 nM. Values for **19** relative to other NMDA antagonists are summarized Table 2.

Antagonism of the NMDA response was noncompetitive in nature. Thus, in the presence of a fully effective concentration of **19**, increasing the concentration of NMDA could not restore the functional response. Inhibition of the cGMP functional response was due to an action of **19** at the glycine recognition site in that it was readily reversible by addition of an excess amount of the glycine-mimetic D-serine. Compound **19** (1 μM) completely inhibited the NMDA response. Addition of D-serine resulted in a concentration-dependent restoration of the NMDA response. With a concentration of D-serine equal to 14.5 μM 50% restoration was achieved. These results indicate that **19** is a noncompetitive inhibitor of NMDA, and therefore the potency of **19** would be unaffected by ischemia-induced elevations of extracellular glutamate.

In Vivo Activity. Following the characterization of the in vitro activity, several critical issues were addressed using a series of in vivo models. In vivo evidence of NMDA antagonism was obtained in mice by monitoring effects of intravenously administered compound **19** on harmaline-induced elevations of cerebellar cGMP content. Harmaline is known to activate the climbing

Table 2. Summary of Activities for NMDA Antagonists in Tests Used for Compound Selection

	in vitro tests, IC_{50},[a] nM		in vivo functional tests, ED_{50},[a] mg/kg			
compd	binding affinity,[b] nM	functional potency (cGMP)[c]	harmaline increase in cGMP, mouse, iv	audiogenic seizures, DBA/2J,[d] mouse, ip	quinolinic acid seizures,[d] mouse, iv	maximal electroshock, rat, iv
1	10.9	282	59	12.2	37.0	29.0
19	24.3	364	15	10.8	14.9	30.6
11h	9.6	87	35	18.6	29.5	54.1
21a	462	2560	>64	16.9	55.0	>128
21c	114	840	>64	8.5	>64	>128
38	20	183	3.5	3.7	14.7	46.3
39	15.2	262	nd	>25	>64	>32
40	13.2	31	<0.05	1	5.2	3.5

[a] Numbers reported are the mean of two or more experiments unless indicated. Standard errors are ±10−30% of the mean. [b] IC50 values represent the concentration of the compound required to reduce the binding of the tritiated ligand by 50% for rat cortical and hippocampal membrane strychnine-insensitive gycine binding sites. [c] Inhibition of glutmatate stimulated accumulation of cyclic GMP in neonatal rat cerebral slices. [d] DBA and QAS models were used to assess CNS penetration. The ED_{50} is defined as that dose protecting 50% of the mice.

fiber afferent pathway to the cerebellum that utilizes glutamate as its neurotransmitter. This provides a means for in situ activation of NMDA receptors and thus is an in vivo counterpart of the cGMP assay performed with cerebellar slices. Compound **19** inhibited the harmaline response with an ED_{50} of 15 mg/kg. Comparative data are provided for compound **11h** and reference NMDA antagonists in Table 2.

To demonstrate brain penetration, the audiogenic seizure-prone mouse (DBA/2J) was treated intraperitoneally with compound **19** followed by presentation of a loud sound stimulus (110 dB, 11 kHz, 25 s) to initiate the onset of convulsions. Compound **19** provided protection in this model with an ED_{50} = 10.8 mg/kg. This model is known to be sensitive to NMDA antagonists and has been used as an initial test by a number of pharmaceutical companies developing these compounds.

Compound **19**, when given iv, antagonized the seizures induced by the intracerebroventricular (icv) administration of quinolinic acid, an NMDA agonist, with an ED_{50} = 14.9 mg/kg. This value is consistent with the dose range for biochemical activity of **19** as an antagonist at the NMDA receptor (i.e. harmaline-elevated cGMP). A time course analysis found that 20.7 mg/kg of compound **19** protected 60% of the mice at 5 min after injection, 20% at either 1 or 2 h, and 0% at 4 h. Thus, compound **19** had a peak effect at 5 min with duration of approximately 1 h after injection in mice.

In the rat, compound **19** antagonized maximal electroshock-induced seizures with an ED_{50} = 30.6 mg/kg iv. A time course analysis found that 54.7 mg/kg of **19** protected 70% of the rats at 5 min and 10% at 1 h after iv injection. Thus, the duration of effect in rats is similar to that seen in the mouse vide supra. These tests enabled the selection of compound **19** for evaluation in the stroke model and provided guidance for the conditions used in the animal stroke experiments

Summary of in Vitro and in Vivo Data on Compound 19 Used To Make Compound Selection. Table 2 summarizes the key data used to choose compound **19** for advancement. Key competitors and compounds of interest are **38** (CoCensys/Ciba), **39** (Glaxo Wellcome), and **40** (Merck), which are currently in late-phase clinical trials for the treatment of stroke. In mouse behavioral tests or in mouse-derived tissues, **38** was as potent or 2−3-fold more potent than **19**. However, in the rat, **19** was more potent in the maximal electroshock seizure test. Thus, both compounds **19** and **38** show a similar broad pattern of efficacy in seizure models. In contrast, **39** is a potent receptor antagonist in in vitro tests; however, this compound exhibited no activity following iv or ip administration. Activity was detected in these tests following direct administration into the brain (icv). These data are consistent with a limited penetration of **39** into the intact nervous system. Further evaluation of these competing compounds will focus on their comparative activity in the stroke models.

The selection of compound **19** for evaluation in a therapeutic model of stroke was derived by a logical demonstration of glycine/NMDA receptor antagonism, from initial binding studies, and through functional assays, to in vivo activities.

Activity in the Stroke Model. Stroke is defined as a focal neurological deficit that is sudden in onset and stable over time. It is caused by an interruption in blood flow through a cerebral vessel and may be thrombotic, embolic, or hemorrhagic in origin. The resulting neurological damage is related to the density of ischemia (i.e., residual blood flow in the ischemic zone) and its duration. Because of the inherent variability of the human condition, two different animal models of focal cerebral ischemia were chosen to represent the disease, dMCAo (distal middle cerebral artery occlusion) and pMCAo (proximal middle cerebral artery occlusion). These models, and their key features are outlined in Table 3.

The models were chosen to represent the human disease by providing a range of ischemic insult severity. Thus, the dMCAo model, using permanent ischemia in a strain with little collateral circulation, gives a severe ischemia with only a small fraction of salvageable tissue. In contrast, the pMCAo, using a 3 h period of ischemia, followed by reperfusion in a strain with good collateral circulation, provides a model of moderately severe ischemia with a high fraction of salvageable tissue. Consistent with these features, postischemic administration of compound **19** reduced infarct volume by 28% in the dMCAo and 77% in the pMCAo models. These data indicate that compound **19** shows a clear pattern of neuroprotection in animal models believed to be predictive of effectiveness in human stroke.

Compound **19** reduced infarct volume in both permanent and ischemia-reperfusion models (Table 4). In either model, similar reductions in infarct volume were

Table 3. Summary of the Properties of the Stroke Models Used To Evaluate Antagonist **19**

feature	dMCAo[a]	pMCAo[b]
animal/strain	rat/spontaneously hypertensive (SH rat)	rat/Wistar
location arterial occlusion	distal segment of MCA	proximal segment of MCA
type of "block"	electrocautery	monofilament
duration of ischemia	permanent	temporary (3 h)
density of ischemia	high, little collateral flow	moderate, good collateral flow + reperfusion
severity of ischemia	high	moderate
typical lesion volume	160 mm^3, 11% of hemisphere volume	190 mm^3, 21% of hemisphere volume
brain areas affected	cerebral cortex	cortex and striatum
typical infarct reduction by neuroprotectants	20%	50%

[a] dMCAo = distal middle cerebral artery occlusion. [b] pMCAo = proximal middle cerebral artery occlusion.

Table 4. Summary of Results with Compound **19**

dosing regimen					neuroprotection (% infarct reduction)	
bolus (mg/kg)	infusion (mg/kg/h)	duration (h)	total dose (mg/kg)	initiation (min)	dMCAo (%)	pMCAo (%)
70	70	6	490	−15	32[a]	73[a]
70	70	6	490	30	nd	77[a]
35	35	6	245	30	nd	68[a]
17.5	17.5	6	123	30	nd	49[a]
8.8	8.8	6	62	30	nd	48[a]
4.5	4.5	6	31.5	30	nd	40[a]
2.3	2.3	6	16	30	nd	12
35	35	6	245	30	nd	57[a]
35	35	6	245	30	nd	76[a]
35	35	6	245	30	nd	71[a]
35	35	6	245	120	nd	50[a]
35	35	6	245	180	nd	41[a]
35	35	6	245	240	nd	9
35	35	6	245	240	nd	44[a]
35	35	6	245	360	nd	58[a]
35	35	6	245	360	nd	59[a]
35	35	6	245	480	nd	13
35	35	6	245	−15	13	nd
18	18	6	126	−15	0	nd
35	25	4	135	30	28a	nd

[a] $p < 0.05$.

Table 5. Summary of Results with Competitors

	dosing regimen					neuroprotection (% infarct reduction)	
compd	bolus (mg/ kg)	infusion (mg/kg/h)	duration (h)	total dose (mg/kg)	initiation (min)	dMCAo (%)	pMCAo (%)
38	10	7	6	52	−15	18[a]	50[a]
38	10	7	6	52	30	33[a]	nd
38	10	7	6	52	30	24[a]	nd
38	10	7	6	52	180	nd	28
39	30			30	−15	0	−25[b]
39	30			30	180	nd	32

[a] $p < 0.05$. [b] Indicates increased infarct volume with **39** treatment (not significant).

observed whether the drug was given prior to or following the ischemic insult. Compound **19** was also compared to benchmark NMDA antagonists in the two models (Table 5). In every case, the extent of efficacy observed with compound **19** was greater than that produced by the reference compounds. While the dose for the benchmarks was fully efficacious on the basis of published data, the greater efficacy seen with compound **19** may reflect selection of a suboptimal dose of the reference compounds. Alternatively, the results could indicate a greater degree of efficacy for compound **19** in the therapeutic models.

Conclusions

Analogue **19** is the most fully characterized of the new compounds, being generally more potent than **1** and showing efficacy in the stroke model which differentiates this compound from **1**. The 3-thienyl analogue **11h** is one of the most potent compounds tested to date in the binding assay but is not as active overall as **19**. All of the compounds prepared showed good to excellent binding activity ($\ll$10 μM, the minimal acceptable binding affinity) against [^{3}H]glycine on the NMDA receptor and several compounds, **21a** and **21c**, show potent activity in the DBA/2J model. Compound **19** has a $T_{1/2} > 1$ h following iv administration.

As predicted by the CoMFA analysis, significant increase in binding affinity and potency were obtained by the incorporation of an aromatic group with an electron-withdrawing subtituent or heterocycle at the 2-position of the 3-propenyl moiety of lead structure **1**. Although CoMFA analysis indicated that racemic compound **36** and related dihydro analogues may have significantly improved binding activity, upon biological evaluation they were not any more potent or have better in vivo efficacy than compound **1** to warrant further investigation of this series.

Experimental Section

General Methods. Except where noted otherwise, reagents and starting materials were obtained from common commercial sources and used as received. Anhydrous solvents were purchased from Aldrich Chemical Co., Inc. in *Sure/Seal* bottles. Other reaction solvents and chromatographic, recrystallization, and workup solvents were spectroscopic grade and used as received. When required, reactions were run under an atmosphere of dry nitrogen or argon in oven-dried flasks.

The phrase "concentrated in vacuo" indicates rotary evaporation on a Buchi apparatus at 25−50 °C and 15−20 Torr (water aspirator) or 30 mmHg (KNF Neuberger Model UN 726.12FTP diaphragm pump), unless stated otherwise. Room temperature is abbreviated as "rt". Vacuum drying was performed at <10 Torr at the temperatures noted. Melting points were determined on a Thomas-Hoover Uni-melt capillary melting point apparatus. Melting points and boiling points are reported uncorrected.

Thin-layer chromatography (TLC) was performed on glass-backed, silica gel 60F-254 plates (EM) coated to a thickness of 0.25 mm. The plates were eluted with solvent systems (v/v) as described and visualized by iodine vapor, UV light, or a staining reagent such as $KMnO_4$ solution.[29] Gas chromatography (GC) was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a Hewlett-Packard 3392A integrator. Separations were carried out on a 15 m × 0.32 mm i.d. fused silica capillary column (DB-5, 0.25 mm film) from J & W Scientific. Reversed-phase high-performance liquid chromatographic (HPLC) analyses were performed on a Waters system composed of a Model 600E pump, a Model 486 detector, and a Model 746 data module. The column (250 mm × 4.6 mm i.d.), from Eka Nobel (Nobel Industries, Sweden), was packed with C_8 Kromasil (spherical 13 μm particles, KR100-13-C8). The mobile phase consisted of CH_3CN buffer mixtures, the buffer being made up of 900 parts distilled water, 100 parts CH_3CN, and 1 part TFA. Preparative TLC was performed on glass-backed silica gel 60F-254 plates (EM) coated to a thickness of 2 mm. Preparative radial TLC was accomplished using a Chromatotron (Harris Industries) system. Flash chromatography was carried out using EM Science silica gel 60 (40−63 mm) according to the literature procedure[30] using the solvent systems as described.

Infrared (IR) spectra were recorded on a Mattson Galaxy Series 5020 infrared spectrophotometer with samples prepared as indicated and are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on Varian Gemini-300, Unity-300, Unity-400, or UnityPlus-500 spectrometers with chemical shifts (δ) reported in parts per million (ppm) relative to internal tetramethylsilane (0.0 ppm) or residual protonated solvent (chloroform, 7.26 ppm; dimethyl sulfoxide (DMSO), 2.50 ppm) as a reference. Signals were designated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentuplet), m (multiplet), and br (broad), etc. Coupling constants (J) are reported in hertz. First-order analyses of spectra were attempted when possible; consequently, chemical shifts and coupling constants for multiplets may only be approximate. ^{13}C NMR spectra were recorded on the Varian Gemini or Unity instruments (75 or 100 MHz), with chemical shifts (δ) reported in ppm relative to $CDCl_3$ (77.0 ppm) unless stated otherwise. Mass spectra (MS) were obtained on a Finnigan MAT Model TSQ 700 mass spectrometer system by chemical ionization at 120 eV using methane (CI, 120 eV) unless otherwise indicated as for example with electron impact, MS (EI, 70 eV). The relative peak height in percent for the base peak and the molecular ion designated as M are given in parentheses. High-resolution mass spectrometric analysis (exact mass spectra) was performed in the FAB mode at a mass resolution of 10 000 (10% valley definition) using a VG-Fisons Autospec mass spectrometer. Exact mass values were determined for the protonated molecular ions ($M^+ + 1$). Ultraviolet (UV) spectra were recorded on a Perkin-Elmer Lambda 4C spectrophotometer and reported in nanometers (nm). The sample was prepared in the solvent indicated at a concentration expressed as milligrams per milliliter. The absorptivity (A) and molar absorptivity (ϵ) are calculated at appropriate wavelengths.

Abbreviations: Et_3N, triethylamine; *p*-TsOH, *para*-toluenesulfonic acid; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TMSOTf, trimethylsilyl triflate; TBDMS, *tert*-butyldimethylsilyl; EDC, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride; HOBT, 1-hydroxybenzotriazole hydrate; Tf_2O, trifluoromethanesulfonic anhydride; LiHMDS, lithium hexamethyldisilazide.

Dibromo(diethoxyphosphoryl)acetic Acid *tert*-Butyl Ester,[15] 3. Fresh NaOBr was prepared via dropwise addition of Br_2 (40.0 g, 12.8 mL, 0.25 mol) to a cooled (ice bath), stirred solution of NaOH (20.0 g, 0.5 mol) in H_2O (60 mL). After 25 min *tert*-butyldiethylphosphonoacetate (13.5 g, 12.6 mL, 0.053 mol) was added dropwise over 5 min at ice-bath temperature. When the addition was complete, the mixture was extracted with CH_2Cl_2 (2 × 70 mL) and the combined extracts were washed with H_2O (1 × 100 mL), dried ($MgSO_4$), and concentrated to give **3** as a colorless oil (20.9 g, 95%), $R_f = 0.25$, 50% Et_2O/hexane. ^1H NMR (300 MHz, $CDCl_3$): δ 4.38 (m, 4H), 1.54 (s, 9H, *t*-Bu), 1.40 (overlapping t, 6H, $J = 7.1$ Hz).

Bromo(diethoxyphosphoryl)acetic Acid *tert*-Butyl Ester,[15] 4. To a stirred, cooled (ice bath) solution of the dibromophosphonoacetate **3** (20.8 g, 0.05 mol) in *t*-BuOH (100 mL) was added, in portions, a solution of $SnCl_2 \cdot 2H_2O$ (11.0 g, 0.049 mol) in H_2O (100 mL). The cloudy white reaction mixture was stirred at ice-bath temperature for 15 min and then extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give **4** as a pale yellow oil (15.2 g, 91%), $R_f = 0.24$, 50% Et_2O/hexane. ^1H NMR (300 MHz, $CDCl_3$): δ 4.24−4.31 (m, 5H, 2 CH_2, overlapping d, $J = 15.2$ Hz, CHBr), 1.51 (s, 9H, *t*-Bu), 1.35−1.40 (overlapping t, 6H, $J = 7.0$ Hz).

4,6-Dichloro-3-formyl-1*H*-indole-2-carboxylic Acid Ethyl Ester, 6. To a stirred suspension of 4,6-dichloro-1*H*-indole-2-carboxylic acid ethyl ester (**5**)[14] (20.0 g, 0.077 mol) in anhydrous CH_2Cl_2 (100 mL) and DMF (9.0 mL, 0.117 mol) at rt was added $POCl_3$ (18.0 g, 11.0 mL, 0.117 mol). The mixture was then heated at reflux for 2.5 h, after which time it was allowed to cool to rt and the precipitate filtered and washed sparingly with H_2O. The crude solid was then treated with 1 M NaOAc/H_2O (300 mL) and stirred at rt for 1 h, filtered, washed with H_2O, and placed under high vacuum (0.5 Torr) for 16 h to afford **6** (14.3 g, 64.7%) as an off-white solid: mp 216−217 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 10.80 (s, 1H), 9.40 (br s, 1H, NH), 7.39 (s, 1H, Ar), 7.35 (s, 1H, Ar), 4.52 (q, 2H, $J = 7.2$ Hz), 1.47 (t, 3H, $J = 7.1$ Hz).

4,6-Dichloro-3-formyl-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 7. To a stirred suspension of **6** (14.3 g, 0.057 mol), K_2CO_3 (32.1 g, 0.23 mol), and DMF (200 mL) at rt was added *p*-TsCl (10.9 g, 0.057 moL) in portions (a slight exotherm was observed). After stirring for 30 min at rt, the mixture was diluted with H_2O (100 mL) and the solid precipitate filtered and washed with additional H_2O. This crude solid was then triturated with Et_2O (100 mL), filtered, and dried under vacuum (0.5 Torr) to yield **7** (18.5 g, 84%) as a white powder: mp 189−191 °C (dec). ^1H NMR (300 MHz, $CDCl_3$): δ 10.71 (s, 1H), 8.00 (m, 3H), 7.36 (m, 3H), 4.61 (q, 2H, $J = 7.2$ Hz), 2.41 (s, 3H), 1.49 (t, 3H, $J = 7.1$ Hz).

(*Z*)-3-(2-Bromo-2-(*tert*-butoxycarbonyl)vinyl)-4,6-dichloro-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl ester, 8. To a stirred solution of **4** (15.2 g, 0.046 mol) in dry THF (200 mL) at −78 °C under N_2 was added LiHMDS (1 M in THF, 45.9 mL, 0.046 mol) dropwise over 10 min. This was followed by the portionwise addition of aldehyde **7** (13.0 g, 0.029 mol) as a suspension in THF (50 mL). The mixture was stirred at −78 °C for 30 min and then allowed to warm to rt and stirred for an additional 1.5 h. A clear dark mixture resulted that was quenched with H_2O (100 mL) and concentrated to remove the THF. The residual oil was then diluted with CH_2Cl_2 (100 mL), washed with H_2O (1 × 50 mL) followed by brine, dried ($MgSO_4$), and concentrated in vacuo to give an amber oil which solidified upon standing. Recrystallization from Et_2O afforded the desired *Z* isomer of **8** (9.6 g, 53%) as a

white solid: mp 131−132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.95 (m, 3H), 7.30 (m, 3H), 4.42 (q, 2H, J = 7.2 Hz), 2.41 (s, 3H), 1.56 (s, 9H, tBu), 1.36 (t, 3H, J = 7.1 Hz). Anal. $C_{25}H_{24}BrCl_2SNO_6$: C, H, N. The ***E*** isomer was obtained by slow fractional crystallization of the mother liquor from EtOAc/cyclohexane to afford vinyl bromide **8*E*** as large colorless rods: mp 117−119.5 °C. ^{1}H NMR ($CDCl_3$): δ 7.99 (d, 1 H, J = 1.7 Hz), 7.96 (d, 2 H, J = 8.7 Hz), 7.50 (s, 1 H), 7.33 (d, 2 H, J = 8.7 Hz), 7.27 (d, 1 H, J = 1.7 Hz), 4.42 (q, 2 H, J = 7.2 Hz), 2.41 (s, 3 H), 1.39 (t, 3 H, J = 7.2 Hz), 1.00 (s, 9 H)—trace Et_2O present.

General Procedure I for Suzuki−Miyaura Coupling Reaction.[13c] Method A. To a stirred suspension of the vinyl bromide **8*Z*** (1.08 g, 1.75 mmol), arylboronic acid,[16] (2.63 mmol) and K_2CO_3 (0.483 g, 3.5 mmol) in toluene (20 mL) under N_2 was added $Pd(PPh_3)_4$ (0.20 g, 10 mol %), and the mixture was heated to 90 °C for 1 h. After 1 h the mixture was concentrated and then diluted with CH_2Cl_2, washed successively with H_2O, saturated $NaHCO_3$, saturated tartaric acid, and then brine, dried ($MgSO_4$), and concentrated to give a yellow-orange semisolid which was immediately flash-chromatographed using 25% Et_2O/hexane on SiO_2 to provide the Suzuki coupled product.

Method B. Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (412 mg, 0.450 mmol) and tri-2-furylphosphine (837 mg, 3.60 mmol) were added to dry THF (60 mL) with stirring under N_2. After 5 min, vinyl bromide **8*Z*** (1.856 g, 3.01 mmol), the electron-rich arylboronic acid (9.20 mmol), and powdered K_2CO_3 (1.27 g, 9.20 mmol) were added to the yellow-green suspension. The reaction mixture was stirred at 55−60 °C for 6−9 days, then cooled to rt, and diluted with cyclohexane (120 mL). The mixture was poured onto a 100 mm × 70 mm SiO_2 column (prepacked with 3:1 cyclohexane/EtOAc) and eluted with 3:1 cyclohexane/EtOAc. The eluant was concentrated in vacuo and the residue purified by flash chromatography (4:1 cyclohexane/EtOAc) to give the Suzuki coupled product.

(*E*)-3-(2-*(tert*-Butoxycarbonyl)-2-phenylvinyl)-4,6-dichloro-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 9a. Phenylboronic acid (0.32 g, 2.63 mmol) was coupled to **8** using general procedure I, method A, to afford **9a** (388 mg, 36.3%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.81 (s, 1H), 7.62 (m, 2H), 7.02−7.26 (m, 8H), 4.12 (q, 2H, J = 7.1 Hz), 2.39 (s, 3H), 1.53 (s, 9H, tBu), 1.24 (t, 3H, J = 7.4 Hz). Anal. $C_{31}H_{29}Cl_2SNO_6$: C, H, N.

(*E*)-3-(2-Carboxy-2-phenylvinyl)-4,6-dichloro-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 10a. *tert*-Butyl ester (**9a**; 388.0 mg, 0.63 mmol) was hydrolyzed with TFA (1.5 mL) in CH_2Cl_2 (20 mL) with stirring at rt for 15 min. The mixture was diluted with additional CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated to give **10a** (345 mg, 98%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (br s, 1H), 8.09 (s, 1H), 7.91 (s, 1H), 7.62 (d, 2H, J = 8.4 Hz), 7.07−7.27 (m, 8H), 4.14 (q, 2H, J = 7.2 Hz), 2.38 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz).

(*E*)-3-(2-Carboxy-2-phenylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11a from Diester 9a via Acid 10a. Vinyl bromide **8*Z*** (928 mg, 1.50 mmol) was coupled with phenylboronic acid (445 mg, 2.59 mmol) using general procedure I, method A, to afford diester **9a**. Removal of the *tert*-butyl ester was accomplished by stirring **9a** in TFA (7 mL) for 1 h. Workup followed by flash chromatography (95:4:1 CH_2Cl_2/MeOH/HOAc) provided acid **10a**, which was hydrolyzed using LiOH·H_2O (122 mg, 2.91 mmol, 3.4 equiv) in 9:1 THF/H_2O (20 mL) at reflux for 7.5 h followed by recrystallization from cyclohexane/EtOAc to provide **11a** as an ivory powder. ^{1}H NMR (DMSO-d_6): δ 12.95 (bs, 2 H), 12.14 (s, 1 H), 8.10 (s, 1 H), 7.32 (s, 1 H), 7.15 (s, 1H), 7.08 (m, 3 H), 6.97 (m, 2 H).

3-(2-Carboxy-2-(naphthalen-1-yl)vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11b from Diester 9b via Acid 10b. Vinyl bromide **8*Z*** (928 mg, 1.50 mmol) was coupled with 1-naphthaleneboronic acid (445 mg, 2.59 mmol) using general procedure I, method A, to afford diester **9b** (453 mg, 45%). ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1 H), 7.87 (d, 1 H, J = 1.7 Hz), 7.7−7.8 (m, 3 H), 7.4−7.5 (m, 5 H), 7.29 (d, 1 H, J = 1.7 Hz), 7.1−7.2 (m, 3 H), 7.00 (dd, 1 H, J = 7.0, 1.1 Hz), 3.63 (bm, 1 H), 2.79 (bm, 1 H), 2.35 (s, 3 H), 1.40 (s, 9 H), 0.79 (t, 3 H, J = 7.2 Hz)—cyclohexane, aromatic impurity present.

Removal of the *tert*-butyl ester was accomplished by stirring **9b** in TFA (7 mL) for 1 h. Workup followed by flash chromatography (95:4:1 CH_2Cl_2/MeOH/HOAc) provided acid **10b** (527 mg) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 9.60 (bs, 1 H), 8.35 (s, 1 H), 7.85 (d, 1 H, J = 1.7 Hz), 7.72−7.8 (m, 3 H), 7.44 (d, 2 H, J = 8.4 Hz), 7.4 (m, 2 H), 7.29 (d, 1 H, J = 1.7 Hz), 7.25 (m, 1 H), 7.14 (d, 2 H, J = 8.0 Hz), 7.07 (dd, 1 H, J = 7.1, 1.1 Hz), 3.7 (bm, 1 H), 2.95 (bm, 1 H), 2.34 (s, 3 H), 0.83 (t, 3 H, J = 7.1 Hz)—cyclohexane and EtOAc present. MS: *m/z* 610, 608 (M^+ + 1), 564, 562, 438, 436, 157 (100).

Hydrolysis of acid **10b** (527 mg, 0.866 mmol) using LiOH·H_2O (122 mg, 2.91 mmol, 3.4 equiv) in 9:1 THF/H_2O (20 mL) at reflux for 7.5 h followed by recrystallization from cyclohexane/EtOAc provided **11b** as an ivory powder: mp 265 °C (dec). IR (KBr): ν_{max} 3252, 1696, 1248, 1235, 777 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.8 (bs, 2 H), 11.96 (s, 1 H), 8.33 (s, 1 H), 7.83 (d, 1 H, J = 8.3 Hz), 7.76 (d, 1 H, J = 8.0 Hz), 7.67 (dd, 1 H, J = 7.3, 2.0 Hz), 7.2−7.40 (m, 4 H), 7.21 (d, 1 H, J = 1.7 Hz), 7.15 (d, 1 H, J = 1.7 Hz)—MeCN and EtOAc present. MS: *m/z* 438, 436 (M^+ + 29 − H_2O), 427, 426 (M^+ + 1), 425 (M^+), 410, 408 (100), 382, 380. Anal. $C_{22}H_{13}Cl_2NO_4$: C, H, N.

3-[2-Carboxy-2-(2,4-dichlorophenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11c from Diester 9c via Acid 10c. Vinyl bromide **8*Z*** (821 mg, 1.33 mmol) was coupled with (2,4-dichlorophenyl)boronic acid (382 mg, 2.00 mmol) via general procedure I, method A. Flash chromatography (6:1 cyclohexane/EtOAc) gave diester **9c** (500 mg) as an ivory powder: mp 160.5−163.5 °C. IR (KBr): ν_{max} 1723, 1370, 1277, 1196, 1181, 1159, 579 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1 H, J = 1.7 Hz), 7.91 (s, 1 H), 7.62 (d, 2 H, J = 8.4 Hz), 7.35 (d, 1 H, J = 2.0 Hz), 7.28 (d, 1 H, J = 1.4 Hz), 7.23 (d, 2 H, J = 8.4 Hz), 6.86 (dd, 1 H, J = 8.3, 1.9 Hz), 6.75 (d, 1 H, J = 8.3 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 2.40 (s, 3 H), 1.49 (s, 9 H), 1.43 (s, cyclohexane), 1.28 (t, 3 H, J = 7.1 Hz). MS: *m/z* 712, 710 (M^+ + 29), 684, 682 (M^+ + 1), 628, 530, 474, 456, 454, 157 (100). Anal. $C_{31}H_{27}Cl_4NO_6S$: C, H, N.

Removal of the *tert*-butyl ester (vide supra) afforded acid **10c** (389 mg, 47%) as fine ivory granules: mp 202−206 °C (physical change ∼150 °C). IR (KBr): ν_{max} 1730, 1697, 1373, 1273, 1196, 1181, 581 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1 H), 7.95 (d, 1 H, J = 1.7 Hz), 7.62 (d, 2 H, J = 8.4 Hz), 7.36 (d, 1 H, J = 2.0 Hz), 7.29 (d, 1 H, J = 1.7 Hz), 7.24 (d, 2 H, J = 8.3 Hz), 6.93 (dd, 1 H, J = 8.3, 2.1 Hz), 6.83 (d, 1 H, J = 8.3 Hz), 4.26 (q, 2 H, J = 7.2 Hz), 2.40 (s, 3 H), 1.43 (s, cyclohexane), 1.28 (t, 3 H, J = 7.2 Hz). MS: *m/z* 628, 626 (M^+ + 1, with 4 Cl), 582, 456, 454, 157 (100). Anal. $C_{27}H_{19}Cl_4NO_6S\cdot{}^1/_2C_6H_{12}$: C, H, N.

Hydrolysis of **10c** (421 mg, 0.671 mmol) gave diacid **11c** as a fine ivory solid, which was dried under vacuum at 110 °C: mp 251 °C (dec). IR (KBr): ν_{max} 1694, 1240, 1215 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.9 (bs, 2 H), 12.20 (s, 1 H), 8.18 (s, 1 H), 7.42 (d, 1 H, J = 2.2 Hz), 7.33 (d, 1 H, J = 1.8 Hz), 7.18 (d, 1 H, J = 1.8 Hz), 7.15 (dd, 1 H, J = 8.3, 2.2 Hz), 6.94 (d, 1 H, J = 8.3 Hz), 1/6 mol EtOAc present. MS: *m/z* 446, 444 (M^+ + 1, with 4 Cl), 430, 428 (100), 426 (M^+ + 1 − H_2O, with 4 Cl), 190, 99, 85. Anal. $C_{18}H_9Cl_4NO_4$: C, H, N.

3-(2-Carboxy-2-(furan-2-yl)vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11d from Diester 9d via Acid 10d. Vinyl bromide **8*Z*** (1.00 g, 1.62 mmol) was coupled with furan-2-boronic acid (270 mg, 2.4 mmol) using general procedure I, method A, to afford diester **9d** (165 mg, 17%). Removal of the *tert*-butyl ester gave crude acid **10d** (0.1 g, 0.2 mmol), which was hydrolyzed to afford **11d** (59 mg, 59%) as an ivory solid: mp 237−239 °C (dec). ^{1}H NMR (DMSO-d_6): δ 13.3 (bs, 1 H), 12.95 (bs, 1 H), 12.32 (s, 1 H), 7.90 (s, 1 H), 7.40 (d, 1 H, J = 1.8 Hz), 7.29 (dd, 1 H, J = 1.7, 0.6 Hz), 7.12 (d, 1 H, J = 1.8 Hz), 6.43 (dm, 1 H, J = 3.4 Hz), 6.31 (dd, 1 H, J = 3.4, 1.8 Hz). MS: *m/z* 368, 367, 366 (M^+ + 1), 365 (M^+), 350, 348 (M^+ + 1 − H_2O), 322, 279 (100), 85.

3-(2-Carboxy-2-(furan-3-yl)vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11e from Diester 9e via Acid 10e. Vinyl bromide **8*Z*** (1.00 g, 1.62 mmol) was coupled with furan-3-boronic acid (270 mg, 2.4 mmol) using general procedure I, method A, to provide diester **9e** (292 mg, 30%) as a tan oil. Removal of the *tert*-butyl ester gave crude acid **10e**, which was hydrolyzed (vide supra) to give **11e** (170 mg, 96%) as an ivory solid: mp 223−225 °C (dec). ^{1}H NMR (DMSO-d_6): δ 13.0 (bs, 2 H), 12.36 (s, 1 H), 7.94 (s, 1 H), 7.48 (m, 1 H), 7.42 (d, 1 H, J = 1.7 Hz), 7.34 (m, 1 H), 7.15 (d, 1 H, J = 1.7 Hz), 5.78 (m, 1 H). MS: *m/z* 368, 367, 366 (M^+ + 1), 365 (M^+), 350, 348 (M^+ + 1 − H_2O, 100).

(*E*)-3-[2-Carboxy-2-(4-chlorophenyl)vinyl]-4,6-dichloro-1*H*-indole-2-caboxylic Acid, 11f from Diester 9f via Acid 10f. Freshly hydrolyzed 4-chlorobenzeneboronic acid (0.41 g, 2.63 mmol) was coupled with **8** using general procedure I, method A, to afford **9f** (595 mg, 52%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.84 (s, 1H), 7.60 (d, 2H, J = 8.6 Hz), 7.23−7.26 (s overlapping d, 3H, J = 9 Hz), 7.07 (q, 4H, J = 8.4 Hz), 4.16 (q, 2H, J = 7.2 Hz), 2.39 (s, 3H), 1.52 (s, 9H, tBu), 1.25 (t, 3H, J = 7.2 Hz). Anal. $C_{31}H_{28}Cl_3SNO_6$: C, H, N.

tert-Butyl ester **9f** (213.0 mg, 0.328 mmol) was hydrolyzed to give **10f** (188 mg, 96%, 3:1 *E*/*Z*) as a white amorphous solid. Further hydrolysis (LiOH·H_2O) gave 114 mg (87%) of the crude diacid as a yellow amorphous solid. Recrystallization from CH_2Cl_2/MeOH afforded diacid **11f** (18 mg, 14%) as a pale yellow solid: mp 252−254 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.1 (bs, 1.5 H), 12.2 (s, 1 H), 8.11 (s, 1 H), 7.34 (s, 1 H), 7.17 (m, 3 H), 6.97 (m, 2 H).

3-(2-Carboxy-2-(thiophen-2-yl)vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11g from Diester 9g via Acid 10g. Thiophene-2-boronic acid (1.12 g, 9.20 mmol) was coupled with vinyl bromide **8** via general procedure I, method B, to give 1.80 g (88%) of diester **9g** (1.80 g, 88%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1 H, J = 1.7 Hz), 7.80 (d, 2 H, J = 8.5 Hz), 7.64 (s, 1 H), 7.27 (d, 2 H, J = 8.5 Hz), 7.23 (d, 1 H, J = 1.7 Hz), 7.16 (dd, 1 H, J = 5.1, 1.2 Hz), 6.83 (dd, 1 H, J = 3.7, 1.2 Hz), 6.75 (dd, 1 H, J = 5.1, 3.7 Hz), 4.24 (q, 2 H, J = 7.1 Hz), 2.39 (s, 3 H), 1.57 (s, 9 H), 1.26 (t, 3 H, J = 7.1 Hz).

Removal of the *tert*-butyl ester afforded **10g** (1.31 g, 77%) as fine ivory crystals: mp 184−187 °C. IR (KBr): ν_{max} 1726, 1696, 1373, 1275, 1206, 1196, 1177 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.2 (bs, 1 H), 7.92 (d, 1 H, J = 1.7 Hz), 7.80 (d, 2 H, J = 8.4 Hz), 7.60 (s, 1 H), 7.57 (d, 1 H, J = 1.7 Hz), 7.44 (d, 2 H, J = 8.4 Hz), 7.40 (dd, 1 H, J = 4.7, 1.5 Hz), 6.84−6.8 (m, 2 H), 4.14 (q, 2 H, J = 7.1 Hz), 2.37 (s, 3 H), 1.13 (t, 3 H, J = 7.1 Hz)—trace cyclohexane present. MS: *m/z* 594, 592 (M^+ + 29), 566, 564 (M^+ + 1, 100), 548, 546 (M^+ + 1 − H_2O), 520, 518, 394, 392. Anal. $C_{25}H_{19}Cl_2NO_6S_2$: C, H, N.

Hydrolysis of acid **10g** (1.24 g, 2.20 mmol) gave **11g** as a bright yellow solid: mp 239−244 °C (dec). IR (KBr): ν_{max} 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.92 (s, 1 H), 7.38 (d, 1 H, J = 1.7 Hz), 7.28 (dd, 1 H, J = 5.1, 1.2 Hz), 7.12 (d, 1 H, J = 1.7 Hz), 6.87 (dd, 1 H, J = 3.7, 1.2 Hz), 6.77 (dd, 1 H, J = 5.1, 3.7 Hz). MS: *m/z* 410 (M^+ + 29), 392, 384, 383, 382 (M^+ + 1), 381 (M^+), 366, 364 (100), 338, 336. Anal. $C_{16}H_9Cl_2NO_4S$: C, H, N.

3-(2-Carboxy-2-(thiophen-3-yl)vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11h from Diester 9h via Acid 10h. Vinyl bromide **8*Z*** (1.85 g, 3.00 mmol) was coupled with thiophene-3-boronic acid (1.16 g, 9.07 mmol) using the general procedure I, method B, to provide after 9 days diester **9h** (1.53 g) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1 H, J = 1.7 Hz), 7.74 (d, 2 H, J = 8.4 Hz), 7.72 (s, 1 H), 7.26 (d, 2 H, J = 8.0 Hz), 7.24 (d, 1 H, J = 1.7 Hz), 7.03 (d, 1 H, J = 4.4 Hz), 7.02 (d, 1 H, J = 1.5 Hz), 6.77 (dd, 1 H, J = 4.7, 1.6 Hz), 4.20 (q, 2 H, J = 7.15 Hz), 2.40 (s, 3 H), 1.55 (s, 9 H), 1.28 (t, 3 H, J = 7.15 Hz).

Diester **9h** was treated with TFA to give acid **10h** (835 mg, 49%) as ivory crystals: mp 197−200 °C (dec). IR (KBr): ν_{max} 1723, 1694, 1373, 1277, 1206, 1196, 1177 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1 H), 7.95 (d, 1 H, J = 1.7 Hz), 7.74 (d, 2 H, J = 8.5 Hz), 7.27 (d, 2 H, J = 8.5 Hz), 7.25 (d, 1 H, J = 1.7 Hz), 7.08 (d, 1 H, J = 2.8 Hz), 7.08 (d, 1 H, J = 3.6 Hz), 6.81 (dd, 1 H, J = 3.6, 2.8 Hz), 4.22 (q, 2 H, J = 7.2 Hz), 2.40 (s, 3 H), 1.28 (t, 3 H, J = 7.2 Hz)—Et_2O present. ^{1}H NMR (DMSO-d_6): δ 13.07 (bs, 1 H), 7.88 (d, 1 H, J = 1.7 Hz), 7.74 (d, 2 H, J = 8.4 Hz), 7.66 (s, 1 H), 7.57 (d, 1 H, J = 1.7 Hz), 7.44 (d, 2 H, J = 8.4 Hz), 7.27 (dd, 1 H, J = 5.0, 2.9 Hz), 7.09 (dd, 1 H, J = 2.9, 1.2 Hz), 6.63 (dd, 1 H, J = 5.0, 1.2 Hz), 4.11 (q, 2 H, J = 7.1 Hz), 2.36 (s, 3 H), 1.14 (t, 3 H, J = 7.1 Hz)—cyclohexane and trace EtOAc present. MS: *m/z* 592 (M^+ + 29), 566, 564 (M^+ + 1), 548, 546 (M^+ + 1 − H_2O), 520, 518, 394, 392, 157 (100), 139. Anal. $C_{25}H_{19}Cl_2NO_6S_2$: C, H, N.

Hydrolysis (vide supra) of acid **10h** (1.147 g, 2.03 mmol) gave **11h** as fine yellow crystals: mp 228−232 °C (dec). IR (KBr): ν_{max} 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.3 (bs, 1 H), 12.8 (bs, 1 H), 12.24 (s, 1 H), 8.01 (s, 1 H), 7.37 (d, 1 H, J = 1.7 Hz), 7.20 (dd, 1 H, J = 5.0, 3.0 Hz), 7.12 (d, 1 H, J = 1.7 Hz), 7.03 (dd, 1 H, J = 3.0, 1.2 Hz), 6.66 (dd, 1 H, J = 5.0, 1.2 Hz). MS: *m/z* 410 (M^+ + 29), 392, 383, 381 (M^+), 366, 364 (100), 338, 336. Anal. $C_{16}H_9Cl_2NO_4S$: C, H, N.

3-[2-Carboxy-2-(4-methoxyphenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 11i from Diester 9i via Acid 10i. Vinyl bromide **8*Z*** (623 mg, 1.01 mmol) was coupled with (*p*-methoxyphenyl)boronic acid (456 mg, 3.00 mmol) using general procedure I, method B, to give diester **9i** (427 mg). ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 1 H, J = 1.7 Hz), 7.75 (s, 1 H), 7.63 (d, 2 H, J = 8.5 Hz), 7.24 (d, 1 H, J = 1.7 Hz), 7.21 (d, 2 H, J = 8.6 Hz), 6.98 (d, 2 H, J = 8.9 Hz), 6.64 (d, 2 H, J = 8.9 Hz), 4.15 (q, 2 H, J = 7.1 Hz), 3.74 (s, 3 H), 2.37 (s, 3 H), 1.53 (s, 9 H), 1.23 (t, 3 H, J = 7.1 Hz). MS: *m/z* 672 (M^+ + 29), 644 (M^+ + 1), 598, 590, 589, 588 (M^+ − C_4H_8, 100), 572, 570.

Removal of the *tert*-butyl ester (vide supra) with 96% HCO_2H (6 mL), followed by recrystallization from cyclohexane/EtOAc gave acid **10i** (276 mg) as light ivory crystals: mp 175−178 °C. IR (KBr): ν_{max} 1728, 1692, 1371, 1271, 1250, 1179 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1 H), 7.92 (d, 1 H, J = 1.7 Hz), 7.63 (d, 2 H, J = 8.5 Hz), 7.26 (d, 1 H, J = 1.7 Hz), 7.22 (d, 2 H, J = 8.5 Hz), 7.01 (d, 2 H, J = 8.8 Hz), 6.67 (d, 2 H, J = 8.9 Hz), 4.16 (q, 2 H, J = 7.2 Hz), 3.76 (s, 3 H), 2.38 (s, 3 H), 1.24 (t, 3 H, J = 7.2 Hz)—trace cyclohexane present. MS (CI, 70 eV): *m/z* 616 (M^+ + 29), 590, 588 (M^+ + 1), 572, 570, 157 (100), 139. Anal. $C_{28}H_{23}Cl_2NO_7S$: C, H, N.

Hydrolysis of acid **10i** (258 mg, 0.438 mmol) gave **11i** as fine yellow needles: mp 252 °C (dec). IR (KBr): ν_{max} 1690, 1611, 1248, 1177 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.5−12.3 (2 H), 12.14 (s, 1 H), 7.99 (s, 1 H), 7.33 (d, 1 H, J = 1.7 Hz), 7.14 (d, 1 H, J = 1.7 Hz), 6.89 (d, 2 H, J = 8.7 Hz), 6.65 (d, 2 H, J = 8.7 Hz) 3.62 (s, 3 H). MS: *m/z* 407 (M^+ + 1), 406, 405 (M^+), 390, 388 (100), 362, 360. Anal. $C_{19}H_{13}Cl_2NO_5$: C, H, N.

(*E*)-4,6-Dichloro-3-(2-phenyl-2-(phenylcarbamoyl)vinyl)-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 12a. To the acid ester **10a** (340 mg, 0.61 mmol) in CH_2Cl_2 (20 mL) at rt was added $SOCl_2$ (80.0 mg, 0.05 mL, 0.671 mmol). After stirring for 15 min, aniline (62.5 mg. 0.061 mL, 0.671 mmol) was added and immediately a white precipitate formed. The reaction was stirred an additional 2 h, diluted with CH_2Cl_2, washed with H_2O, then with 1 N HCl, dried ($MgSO_4$), and concentrated to a yellow oil. Flash chromatography (3:1 hexane/Et_2O) provided **12a** (262 mg, 68%) as a white solid: mp 84−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, 2H, J = 7.9 Hz), 7.61 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.11−7.33 (m, 12H), 4.21 (q, 2H, J = 7.1 Hz), 2.39 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz). Anal. $C_{33}H_{26}Cl_2SN_2O_5$: C, H, N.

4,6-Dichloro-3-(2-(phenylcarbamoyl)vinyl)-1*H*-indole-2-carboxylic Acid, 13a. Hydrolysis (vide supra) of amide ester **12a** (0.68 g, 1.1 mmol) gave **13a** (109 mg, 23%) as an ivory powder: mp 276 °C (dec). IR (KBr): ν_{max} 3397, 3298, 1690, 1616, 1597, 1524, 1441, 1316 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.31 (bs, 1 H), 12.18 (s, 1 H), 9.67 (s, 1 H), 7.81 (s, 1 H), 7.7−7.8 (m, 2 H), 7.3−7.4 (m, 3 H), 7.1 (m, 5 H), 7.0 (m, 2 H)—ether, MeCN, EtOAc present. ^{13}C NMR (DMSO-d_6): δ 166.5, 161.7, 140.6, 139.1, 137.0, 136.2, 129.7, 128.7, 128.5, 127.7, 127.4, 127.3, 127.1, 123.5, 122.2, 120.8, 120.3, 115.9, 111.1. MS: *m/z* 451 (M^+ + 1), 136, 120 (100). Anal. $C_{24}H_{16}Cl_2N_2O_3$: C, H, N.

4,6-Dichloro-3-(2-(benzylcarbamoyl)-2-phenylvinyl)-1*H*-indole-2-carboxylic Acid, 13b from Amide Ester 12b. Acid ester **10a** (443 mg, 0.793 mmol) was reacted with benzylamine (95 mL, 0.87 mmol), HOBT (118 mg, 0.771 mmol), and EDC (167 mg, 0.871 mmol) in CH_2Cl_2 (5 mL) to afford, after recrystallization from CH_2Cl_2/Et_2O, **12b** (0.34 g, 66%) as a white powder: mp 150−153 °C. IR (KBr): ν_{max} 3401, 1730, 1670, 1516, 1371 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1 H, J = 1.7 Hz), 7.83 (s, 1 H), 7.60 (m, 1 H), 7.58 (m, 1 H), 7.1−7.3 (m, 11 H), 7.1 (m, 2 H), 5.89 (t, 1 H, J = 5.7 Hz), 4.54 (d, 2 H, J = 5.7 Hz), 4.21 (q, 2 H, J = 7.1 Hz), 2.38 (s, 3 H), 1.26 (t, 3 H, J = 7.1 Hz)—Et_2O present. ^{13}C NMR ($CDCl_3$): δ 165.9, 160.7, 145.5, 140.6, 138.0, 137.1, 134.3, 134.0, 132.5, 129.8, 129.6, 128.7, 128.6, 128.3, 128.1, 127.8, 127.5, 127.1, 125.7, 125.6, 121.5, 114.0, 62.6, 44.1, 21.7, 13.8. MS: *m/ z* 675 (M^+ + 29), 647 (M^+ + 1), 493, 157 (100), 139. Anal. $C_{34}H_{28}Cl_2N_2O_5S$: C, H, N.

Hydrolysis (vide supra) of amide ester **12b** (0.44 g, 0.68 mmol) afforded **13b** (153 mg, 48%) as a white powder: mp 262 °C (dec). IR (KBr): ν_{max} 3416, 3322, 1674, 1613, 1557, 1526, 1499, 1454, 1236, 1211 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.07 (bs, 1 H), 8.05 (t, 1 H, J = 6.1 Hz), 7.73 (s, 1 H), 7.2−7.3 (m, 6 H), 7.1 (m, 4 H), 6.9−7.0 (m, 2 H), 4.40 (d, 2 H, J = 6.1 Hz). ^{13}C NMR (DMSO-d_6): δ 167.2, 161.7, 140.1, 139.9, 136.8, 136.2, 129.5, 128.5, 128.2, 127.8, 127.5, 127.2, 127.0, 127.0, 126.6, 122.5, 120.6, 115.8, 111.0, 42.7. MS: *m/z* 493 (M^+ + 29), 465 (M^+ + 1), 429, 197. Anal. $C_{25}H_{18}Cl_2N_2O_3$: C, H, N.

4,6-Dichloro-3-(2-(methylcarbamoyl)-2-phenylvinyl)-1*H*-indole-2-carboxylic Acid, 13c from Amide Ester 12c. Acid ester **10a** (800 mg, 1.43 mmol) was reacted (vide supra) with methylamine hydrochloride (116 mg, 1.72 mmol), to afford **12c** (376 mg, 46%) as a white powder. IR (KBr): ν_{max} 3441, 1722, 1514, 1383, 1370 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.84 (m, 1 H), 7.65 (d, 2 H, J = 8.6 Hz), 7.58 (m, 1 H), 7.53 (m, 1 H), 7.41 (d, 2 H, J = 8.6 Hz), 7.33 (s, 1 H), 7.12−7.26 (m, 3 H), 6.93 (m, 2 H), 4.10 (q, 2 H, J = 7.2 Hz), 2.69 (d, 3 H, J = 4.6 Hz), 2.37 (s, 3 H), 1.13 (t, 3 H, J = 7.1 Hz). MS: *m/z* 571 (M^+ + 1), 417 (100), 386, 157. Anal. $C_{28}H_{24}Cl_2N_2O_5S$: C, H, N.

Hydrolysis of amide ester **12c** (335 mg, 0.586 mmol) using LiOH·H_2O (42 mg, 1.0 mmol) in THF (12 mL) and H_2O (5 mL) provided **13c** (58 mg, 25%) as a white powder. IR (KBr): ν_{max} 3421, 3233, 1665, 1632, 1528, 1298, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.25 (bs, 1 H), 12.06 (s, 1 H), 7.66 (s, 1 H), 7.35 (m, 1 H), 7.31 (m, 1 H), 7.10 (m, 4 H), 6.93 (m, 2 H), 2.70 (d, 3 H, J = 4.6 Hz). MS: *m/z* 389 (M^+ + 1, 100), 371, 358, 353. Anal. $C_{19}H_{14}Cl_2N_2O_3$: C, H, N.

3-(2-Carbamoyl-2-phenylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 13d from Amide Ester 12d. Acid ester **10a** (0.77 g, 1.4 mmol) was treated with NH_4Cl and Et_3N (1.1 equiv) to give, after two recrystallizations (CH_2Cl_2/Et_2O), **12d** (233 mg, 30%) as an ivory powder: mp 205−208 °C. IR (KBr): ν_{max} 1728, 1711, 1688, 1593, 1371 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1 H, J = 1.7 Hz), 7.82 (s, 1 H), 7.61 (m, 1 H), 7.58 (s, 1 H), 7.1−7.3 (m, 8 H), 5.63 (bs, 1 H), 5.57 (bs, 1 H), 4.21 (q, 2 H, J = 7.2 Hz), 2.38 (s, 3 H), 1.27 (t, 3 H, J = 7.2 Hz)—Et_2O, CH_2Cl_2 present. ^{13}C NMR ($CDCl_3$): δ 167.7, 160.6, 145.6, 140.0, 137.2, 134.6, 134.0, 132.6, 129.9, 129.7, 129.5, 128.6, 128.6, 128.3, 128.1, 127.1, 125.7, 125.5, 121.3, 114.0, 62.6, 21.7, 13.8. MS: *m/z* 585 (M^+ + 29), 557 (M^+ + 1), 540, 511, 403, 386, 157 (100), 139, 129. Anal. $C_{27}H_{22}Cl_2N_2O_5S$: C, H, N.

Hydrolysis of amide ester **12d** (233 mg, 0.418 mmol) following recrystallization (CH_2Cl_2/Et_2O) afforded **13d** (114 mg, 73%) as a tan powder: mp 169 °C (dec). IR (KBr): ν_{max} 3393, 3283, 1680, 1615, 1578, 1559, 1534, 1240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.24 (bs, 1 H), 12.06 (s, 1 H), 7.71 (s, 1 H), 7.31 (d, 1 H, J = 1.7 Hz), 7.27 (bs, 1 H), 7.1 (m, 4 H), 6.9 (m, 3 H)—Et_2O present. ^{13}C NMR (DMSO-d_6): δ 168.7, 161.7, 140.1, 136.8, 136.5, 129.4, 128.6, 127.9, 127.3, 127.3, 126.8, 122.4, 120.6, 116.2, 111.0. MS: *m/z* 403 (M^+ + 29), 375 (M^+ + 1, 100), 358. Anal. $C_{18}H_{12}Cl_2N_2O_3$: C, H, N.

3-(2-Carbamoyl-2-phenylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 13d from 6 via 23a. A mixture of aldehyde **6** (1.43 g, 5.0 mmol), phenylacetonitrile (0.59 g, 0.60 mL, 5.0 mmol), and 4 drops of piperidine in 95% EtOH (30 mL) were heated at reflux for 16 h. Upon allowing the reaction to cool to rt, the reaction was diluted with Et_2O and the resulting solid was filtered, washed with Et_2O, and dried under vacuum to yield a yellow solid. Recrystallization from acetone/H_2O gave nitrile **23a** (0.765 g, 40%) as a pale yellow solid: mp 215−217 °C (dec). IR (KBr): ν_{max} 3350, 3086, 3059, 3034, 2986, 2939, 2904, 2222, 1730, 1685, 1606, 1558, 1531, 1496, 1475, 1448, 1438, 1421, 1388, 1367, 1342, 1321, 1303 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.81 (s, 1 H), 8.33 (s, 1 H), 7.76 (d, 2 H, J = 7.0 Hz), 7.52 (m, 4 H), 7.35 (s, 1 H), 4.34 (q, 2 H, J = 6.7 Hz), 1.25 (t, 3 H, J = 6.8 Hz)—the NMR suggested the presence of a paramagnetic impurity. MS (EI, eV): *m/z* 384 (M^+), (M^+ − HCO_2Et, 100). Anal. $C_{20}H_{14}Cl_2N_2O_2$: C, H, N.

Nitrile **23a** (225 mg, 0.584 mmol) was heated in H_2SO_4 (3 mL) and HOAc (3 mL) at 70 °C for 16 h. The reaction was allowed to cool to rt and was poured onto H_2O (50 mL), and the resulting solid was filtered, washed with additional H_2O, and dried to give crude amide as a 65:35 *E*/*Z* mixture. Recrystallization from acetone/H_2O provided 212 mg (90%) of the intermediate *E* amide ester as a tan solid: mp 267−270 °C (dec). A solution of amide ester (202 mg, 0.50 mmol) and LiOH·H_2O (42 mg, 1.0 mmol) in 1:1 THF/H_2O (10 mL) was heated at 60 °C for 16 h. The THF was then evaporated and the residue diluted with water and acidified to pH 1 with 6 N HCl. A precipitate formed that was filtered and washed with additional H_2O and washed sparingly with Et_2O. Drying under high vacuum afforded **13d** (136 mg, 73%) as a tan solid, which was an ∼5:1 *E*/*Z* isomeric mixture. Further hydrolysis of amide carboxylic acid **13d** to afford **1** failed by standard hydrolysis methods. For additional information and conditions see ref 22.

4,6-Dichloro-3-(2-(dimethylcarbamoyl)-2-phenylvinyl)-1*H*-indole-2-carboxylic Acid, 13e from Amide Ester 12e. Acid ester **10a** (0.81 g, 1.5 mmol) was reacted (vide supra) with Me_2NH to give **12e** (0.75 g, 88%) as a white powder: mp 73−81 °C. IR (KBr): ν_{max} 1732, 1638, 1389, 1371 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1 H, J = 1.7 Hz), 7.73 (m, 1 H), 7.69 (m, 1 H), 7.1−7.3 (m, 8 H), 6.99 and 6.69 (s, 1 H total, 1:5 ratio), 4.14 (q, 2 H, J = 7.2 Hz), 3.06 and 3.04 and 3.00 (s, 6 H total), 2.39 (s, 3 H), 1.34 and 1.25 (t, 3 H total, J = 7.2 Hz, 1:5 ratio). ^{13}C NMR ($CDCl_3$): δ 170.2, 160.8, 145.6, 143.0, 137.1, 134.5, 134.3, 132.4, 129.9, 128.4, 128.1, 128.0, 128.0, 127.6, 127.3, 125.5, 122.3, 121.1, 120.4, 118.8, 114.0, 110.5, 62.7, 61.6, 38.2, 34.8, 26.9 (C_6H_{12}), 21.7, 14.2, 13.7. MS: *m/z* 585 (M^+ + 1), 431 (100),157. Anal. $C_{29}H_{26}Cl_2N_2O_5S$: C, H, N.

Hydrolysis of amide ester **12e** (0.75 g, 1.3 mmol) gave **13e** (308 mg, 60%) as a white powder. The acid contained 6% of the *Z* isomer by HPLC and NMR. For **13e**: mp 170−176 °C. IR (KBr): ν_{max} 3233, 1692, 1613, 1557, 1534, 1497, 1443, 1402, 1209 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.27 (bs, 1 H), 12.18 (s, 1 H), 7.37 (d, 1 H, J = 1.7 Hz), 7.1 (m, 4 H), 7.0 (m, 2 H), 6.85 (s, 1 H), 3.15 and 2.65 (s, 3 H total, 94:6 ratio), 2.96 and 2.62 (s, 3 H total, 94:6 ratio). ^{13}C NMR (DMSO-d_6): δ 170.1, 161.8, 139.7, 137.1, 136.1, 128.7, 127.8, 127.4, 127.2, 122.3, 121.2, 120.7, 115.6, 111.1, 37.8, 34.2. MS: *m/z* 431 (M^+ + 29), 403 (M^+ + 1, 100), 157. Anal. $C_{20}H_{16}Cl_2N_2O_3$: C, H, N.

4,6-Dichloro-3-(2-(phenethylcarbamoyl)-2-phenylvinyl)-1*H*-indole-2-carboxylic Acid, 13f from Amide Ester 12f. Acid ester **10a** (1.08 g, 1.93 mmol) was reacted with phenethylamine to afford **12f** (0.87 g, 68%) as white needles: mp 108−112 °C. IR (KBr): ν_{max} 1730, 1514, 1371, 1269, 1194, 1181, 665, 581 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1 H, J = 1.7 Hz), 7.75 (s, 1 H), 7.59 (m, 1 H), 7.57 (m, 1 H), 7.1−7.3 (m, 11 H), 6.9−7.0 (m, 2 H), 5.56 (bt, 1 H, J = 5.6 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.58 (q, 2 H, J = 6.5 Hz), 2.82 (t, 2 H, J = 6.8 Hz), 2.37 (s, 3 H), 1.26 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 165.7, 160.6, 145.5, 140.8, 138.6, 137.1, 134.3, 134.0, 132.5, 129.8, 129.5, 128.7, 128.6, 128.4, 128.1, 127.3, 127.1, 126.5, 125.6, 121.5, 114.0, 62.5, 41.1, 35.3, 26.9, 21.6, 13.8. MS: *m/z* 689 (M^+ + 29), 661 (M^+ + 1, 100), 615, 505, 157. Anal. $C_{35}H_{30}Cl_2N_2O_5S$: C, H, N.

Hydrolysis of amide ester **12f** (0.87 g, 1.3 mmol) gave **13f** (321 mg, 51%) of as an ivory powder: mp 232 °C (dec). IR (KBr): ν_{max} 3418, 1611, 1555, 1528, 1447, 1379, 1333, 1281

cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.43 (bs, 1 H), 7.75 (s, 1 H), 7.64 (bs, 1 H), 7.2−7.4 (m, 6 H), 6.97 (s, 5 H), 6.84 (d, 1 H, J = 1.6 Hz), 3.43 (q, 2 H, J = 6.8 Hz), 2.81 (t, 2 H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6): δ 167.9, 139.5, 138.3, 136.8, 136.0, 135.1, 130.0, 128.7, 128.3, 127.0, 126.5, 126.2, 126.0, 122.2, 119.3, 111.1, 40.8, 35.1. MS: *m/z* 507 (M^+ + 29), 479 (M^+ + 1), 435, 240, 148, 105 (100). Anal. $C_{26}H_{20}Cl_2N_2O_3$: C, H, N.

4,6-Dichloro-3-(3-(morpholin-4-yl)-3-oxo-2-phenylpropenyl)-1*H*-indole-2-carboxylic Acid, 13g from Amide Ester 12g. Acid ester **10a** (450 mg, 0.806 mmol) was reacted with morpholine (80 mL, 0.92 mmol) to afford **12g** (411 mg, 81%) as a white amorphous solid. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1 H, J = 1.7 Hz), 7.71 (d, 2 H, J = 8.4 Hz), 7.0−7.3 (m, 8 H), 6.73 (s, 1 H), 4.12 (q, 2 H, J = 7.2 Hz), 3.71 (bs, 4 H), 3.51 (bs, 4 H), 2.40 (s, 3 H), 1.23 (t, 3 H, J = 7.2 Hz). Anal. $C_{31}H_{28}Cl_2N_2O_6S$: C, H, N.

Hydrolysis of amide ester **12g** (337 mg, 0.537 mmol) gave acid **13g** as a white crystalline powder: mp > 275 °C. IR (KBr): ν_{max} 1711, 1605, 1466, 1443 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 13.40 (bs, 1 H), 12.20 (s, 1 H), 7.37 (d, 1 H, J = 1.8 Hz), 7.09−7.15 (m, 4 H), 7.00−7.05 (m, 2 H), 6.90 (s, 1 H), 3.6 (m, 4 H-overlapping H_2O peak), 3.33 (bs, 4 H). MS: *m/z* 485 (M^+ + 41), 475, 473 (M^+ + 29), 447, 446, 445 (M^+ + 1, 100), 206. Anal. $C_{22}H_{18}Cl_2N_2O_4$: C, H, N.

3-(2-(Benzyloxycarbamoyl)-2-phenylvinyl)-4,6-dichloro-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 12h. The reaction (vide supra) of acid ester **10a** (0.77 g, 1.4 mmol) with *O*-benzylhydroxylamine hydrochloride and Et_3N (1.2 equiv) afforded **12h** (1.33 g, 96%) as a yellow powder: ~7:1 *E/Z* ratio. IR (KBr): ν_{max} 3422, 1730, 1678, 1371, 1271, 1194, 1177, 1007, 700, 665, 581 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.25 and 11.16 (major) (2s, 1 H), 7.86 (major) (d, 1 H, J = 1.7 Hz), 7.7 (m, 2 H), 7.59 (major) (d, 1 H, J = 1.7 Hz), 7.3−7.5 (m, 7 major and 9 minor H), 7.1−7.2 (m, 4 H), 6.8−6.9 (m, 2 H), 4.9 (m, 2 H), 4.14 and 4.06 (major) (2q, 2 H, J = 7.2 Hz), 2.38 (major) (s, 3 H), 1.24 and 1.12 (major) (2t, 3 H, J = 7.2 Hz). MS: *m/z* 691 (M^+ + 29), 663 (M^+ + 1), 509, 403, 386, 157, 107 (100), 91, 79.

4,6-Dichloro-3-(2-(hydroxycarbamoyl)-2-phenylvinyl)-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 12i from Amide Ester 12j. To a solution of the acid ester **10a** (1.28 g, 2.29 mmol) in anhydrous CH_2Cl_2 (10 mL) was added DMF (2 drops) followed by oxalyl chloride (0.28 mL, 3.2 mmol). The reaction mixture was stirred at rt for 45 min. The reaction was concentrated in vacuo, and the residue was taken up in MeCN (6 mL). To this solution at 0 °C was added a solution of *N*-*t*-Boc-*O*-TBDMS hydroxylamine (0.79 g, 3.2 mmol), DMAP (29 mg, 0.23 mmol), and Et_3N (0.45 mL, 3.2 mmol) in MeCN (9 mL). The reaction mixture was allowed to stir at 0 °C for 4 h. The solution was concentrated in vacuo, and the residue taken up in EtOAc, washed with water (2×), and dried ($MgSO_4$). The residue was filtered through a short column of SiO_2 (eluting with CH_2Cl_2) to give **12j** (1.44 g, 69%) as a pale yellow solid. To a solution of **12j** (1.44 g, 1.83 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added CsF (0.31 g, 2.0 mmol) and TFA (3.4 mL, 44 mmol). The reaction mixture was stirred at 0 °C for 5 h, then diluted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). Filtration through SiO_2 (eluting with 5−10% MeOH/$CHCl_3$) afforded **12i** (0.34 g, 32%) as an ivory powder. IR (KBr): ν_{max} 1728, 1597, 1389, 1373, 1269, 1196, 1182, 1090, 1003, 581 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.68 (s, 1 H), 9.04 (m, 1 H), 7.84 (d, 1 H, J = 1.7 Hz), 7.65 (d, 2 H, J = 8.3 Hz), 7.56 (d, 1 H, J = 1.7 Hz), 7.39 (d, J = 8.3 Hz), 7.1−7.2 (m, 4 H), 6.9 (m, 2 H), 4.08 (q, 2 H, J = 7.1 Hz), 2.36 (s, 3 H), 1.12 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ 164.6, 159.7, 146.3, 140.8, 136.3, 134.4, 133.0, 131.8, 130.3, 129.4, 128.9, 127.9, 127.8, 127.8, 126.8, 125.5, 122.3, 120.6, 113.4, 62.2, 21.1, 13.5. MS: *m/z* 573 (M^+ + 1), 540, 529 (100), 499, 483, 386, 375, 157.

General Procedure II for Lewis Acid-Catalyzed Enol Ether Coupling. The respective enol ether was prepared by reacting the desired substituted methyl phenyl acetate (0.023 mol) with NaH (95%, 1.3 g) in THF (50 mL) at 0 °C followed by the addition of HCO_2CH_3 (3.0 mL) and a few drops of MeOH. The reaction was allowed to warm to rt and, after stirring 16 h, was concentrated, diluted with DMF (50 mL), cooled to 0 °C, and treated with MeI (6.8 g, 3 mL, 0.476 mol). After stirring the reaction for 2.5 h at rt, the reaction was diluted with H_2O, extracted with Et_2O, and washed twice with H_2O, dried ($MgSO_4$), and concentrated to give the crude enol ether, which was used without further purification. TMSOTf (2.2 mL, 11.0 mmol) was added dropwise over 10 min followed by the addition of the indole ester **5** (2.82 g, 10.9 mmol) portionwise to the crude enol ether (2.8 g, 0.012 mol) in $ClCH_2CH_2Cl$ (40 mL) at rt. The reaction was heated at 70 °C for 8 h and then concentrated to a dark residue. This was diluted with Et_2O, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to a light brown solid that was chromatographed (hexane: Et_2O: 3:1) to give the diester. The diester was then subjected to base hydrolysis using excess LiOH·H_2O heating to 95 °C overnight to provide the desired diacid.

3-[2-(4-Fluorophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17a from 15a via 16a. (4-Fluorophenyl)acetic acid methyl ester (**14a**; 10.9 g, 94%) was prepared from (*p*-fluorophenyl)acetic acid (10.6 g, 68.8 mmol) as a white solid which was used without further purification.

The enol ether **15a** was generated from **14a** (10.9 g, 64.8 mmol), as described in general procedure II, to afford **15a** (11.2 g, 82%) as a light yellow/green solid: TLC, hexane/EtOAc (2:1), R_f = 0.52. Condensation of enol ether **15a** (1.74 g, 8.28 mmol) with indole **5** (1.94 g, 7.52 mmol), vida supra, afforded **16a** (1.74 g, 53%) as a light yellow solid: TLC, cyclohexane/EtOAc (7:3), R_f = 0.5. IR (KBr): ν_{max} 1721, 1686, 1532, 1350, 1323, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.25−12.40 (bs, 1 H), 8.08 (s, 1 H), 7.42−7.55 (m, 1 H), 7.38 (d, 1 H, J = 1.6 Hz), 7.24 (m, 1 H), 7.20 (d, 1 H, J = 1.6 Hz), 6.89−6.98 (m, 4 H), 4.27 (q, 2 H, J = 7.1 Hz), 3.80 (s, 3 H), 1.25 (t, 3 H, J = 7.1 Hc). ^{19}F NMR (DMSO-d_6): δ −114.04 to −114.14 (m, 1 F). MS: *m/z* 436 (M^+ + 1), 404 (M^+ + 1 − MeOH), 376. Anal. $C_{21}H_{16}Cl_2FNO_4$: C, H, N.

Hydrolysis of *p*-fluoro ester **16a** (900 mg, 2.06 mmol) in THF (12 mL) and MeOH (6 mL) with aqueous 1.0 M NaOH (12 mL, 12.0 mmol) at 70 °C for 2.5 h gave, after recrystallization from EtOAc, **17a** (575 mg, 71%) as a light yellow solid. IR (KBr): ν_{max} 3434, 3281, 1687, 1615, 1510, 1238 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.19 (s, 1 H), 8.08 (s, 1 H), 7.33 (d, 1 H, J = 1.6 Hz), 7.16 (d, 1 H, J = 1.6 Hz), 6.89−6.98 (m, 4 H). ^{19}F NMR (DMSO-d_6): δ −114.65 to +114.75 (m, 1 F). MS: *m/z* 394 (M^+), 376 (M^+ − 18), 348, 174, 130, 85. Anal. $C_{18}H_{10}Cl_2FNO_4$: C, H, N.

(*E*)-3-[2-Carboxy-2-(4-chlorophenyl)-vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17b. Methyl (*p*-chlorophenyl)-acetate (4.4 g, 0.024 mol) was treated as described in general procedure II to afford the crude enol ether **15b** (2.8 g, 52%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.24−7.31 (m, 4 H), 3.74 (s, 3H), 3.65 (s, 3H). Compound **15b** (2.8 g, 0.012 mol) was reacted with **5** to give methyl ethyl ester **16b** (1.2 g, 24%) as a white solid: mp 185−187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.23 (br s, 1H), 8.23 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 6.99−7.10 (m, 4H), 4.31 (q, 2H, J = 7.2 Hz), 3.87 (s, 3H), 1.34 (t, 3H, J = 7.1 Hz). IR (KBr): ν_{max} 3418, 3308, 3099, 3088, 3038, 2984, 2953, 2906, 1701, 1612, 1558, 1531, 1491, 1437, 1394, 1369 cm^{-1}. CIMS (CH^4): *m/e* (rel intens) 482 (M + $C_2H_5^+$, 20), 452 (M + H^+, 70), 420 (M + H − MeOH, 100). Anal. $C_{21}H_{16}Cl_3NO_4$: C, H, N.

Hydrolysis of **16b** (1.1 g, 2.40 mmol) afforded the diacid **17b** (0.90 g, 90%) as a pale yellow solid: mp 252−254 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.1 (br s, 1.5 H), 12.2 (s, 1H), 8.11 (s, 1H), 7.34 (s, 1H), 7.17 (m, 3H), 6.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 161.5, 136.9, 135.6, 134.7, 134.2, 131.6, 131.5, 128.8, 127.1, 127.0, 122.3, 120.9, 115.0, 111.2. IR (KBr): ν_{max} 3429, 3271, 3161, 3099, 3090, 3049, 2694, 2661, 2660, 2615, 2542, 1695, 1635, 1614, 1558, 1535, 1493, 1456, 1435, 1410, 1394, 1369 cm^{-1}. CIMS (CH_4): *m/e* (rel inten) 438 (M + $C_2H_5^+$, 3), 410 (M + H^+, 15). Anal. $C_{18}H_{10}Cl_3NO_4 \cdot 1.0C_3H_6O$: C, H, N.

3-[2-(4-Bromophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17c from 15c via 16c. (4-Bromophenyl)acetic acid methyl ester (**14c**; 4.76 g, 90%) was prepared as an oil from (*p*-bromophenyl)acetic acid (5.0 g, 23

mmol) and used without further purification. The enol ether **15c** was prepared (vide supra) from **14c** (4.76 g, 20.8 mmol) to afford **15c** (5.13 g, 91%) as a colorless oil, which was used without further purification. Condensation of **15c** (5.13 g 18.92 mmol) with indole **5** (4.44 g, 17.2 mmol) provided **16c** (5.54 g, 65%) as a light yellow solid that was used without further purification.

Hydrolysis of **16c** (5.52 g, 11.1 mmol) provided **17c** (2.92 g, 58%) as pale yellow crystals. IR (KBr): ν_{max} 3425, 3049, 1691, 1614, 1558, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.96 (bs, 2 H), 12.21 (s, 1 H), 8.11 (s, 1 H), 7.35 (d, 1 H, J = 1.8 Hz), 7.32 (m, 2 H), 7.29 (m, 2 H), 7.17 (d, 2 H, J = 1.8 Hz). MS: *m/z* 456 (M^+ + 1), 438 (M^+ + H − 18), 410, 286, 206, 123. Anal. $C_{18}H_{10}Cl_2BrNO_4 \cdot H_2O$: C, H, N.

3-[2-(4-Iodophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17d from 15d via 16d. (4-Iodophenyl)acetic acid methyl ester (**14d**; 5.01 g, 94%) was prepared (vide supra) and used without further purification. The enol ether **15d** was prepared from **14d**, (5.01 g, 18.1 mmol) to afford **15d** (5.37 g, 93%) as a yellow oil, which was used without further purification. Condensation of enol ether **15d** (3.84 g, 12.1 mmol) with indole **5** (2.83 g, 11.0 mmol) in 1,2-dichloroethane (30 mL), using TMSOTf (2.30 mL, 12.1 mmol), provided **16d** (4.95 g, 87%, 7:3 ratio of *E*/*Z* isomers) as a white powder: mp 213-215 °C (dec). IR (KBr): ν_{max} 3416, 3306, 1748, 1717, 1614, 1485, 1321, 1294, 1240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.45 (bs, 1 H), 8.14 (s, 1 H), 7.70 and 7.50 (2d, 2 H, J = 8.5 Hz), 7.45 and 7.39 (2d, 1 H, J = 1.7 Hz), 7.22 and 7.21 (2d, 1 H, J = 1.7 Hz), 6.94 and 6.75 (2d, 2 H, J = 8.4 Hz), 4.19 (q, 2 H, J = 7.0 Hz), 3.78 and 3.64 (2s, 3 H), 1.25 (t, 3 H, J = 7.0 Hz). MS: *m/z* 543 (M^+), 512 (M^+ − MeOH), 498, 445, 417, 386, 326, 291, 213. Anal. $C_{21}H_{16}Cl_2INO_4$: C, H, N.

Hydrolysis of the *p*-iodo diester **16d** (0.95 g, 1.8 mmol) afforded **17d** (520 mg, 56%) as a white powder. IR (KBr): ν_{max} 3427, 3312, 3271, 1692, 1613, 1240, 1221 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.09 (bs, 2 H), 12.21 (s, 1 H), 8.11 (s, 1 H), 7.45−7.50 (m, 2 H), 7.35 (d, 1 H, J = 1.8 Hz), 7.17 (d, 1 H, J = 1.8 Hz), 6.75−6.80 (m, 2 H). MS: *m/z* 502 (M^+ + 1), 484, 456, 403, 375, 329. Anal. $C_{18}H_{10}Cl_2INO_4$: C, H, N.

3-(2-Carboxy-2-*p*-tolylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17e from 15e via 16e. *p*-Tolylacetic acid methyl ester (**14e**; 3.38 g, 88%) was prepared as an oil (3.50 g, 23.3 mmol) and used without further purification. The enol ether **15e** was prepared (vide supra) to afford **15e** (2.36 g, 57%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1 H), 7.24 (m, 4 H), 3.57 (s, 3 H), 3.76 (s, 3 H), 2.40 (s, 3 H). Condensation of enol ether **15e** (2.36 g, 11.4 mmol) with indole **5** (1.94 g, 7.52 mmol) provided **16e** (2.73 g, 61%) as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 12.32 and 12.28 (2 s, 1 H), 8.08 (s, 1 H), 7.38 (s, 1 H), 7.2 (s, 1 H), 6.8−7.0 (dd, 4 H), 4.2 (q, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.16 (s, 3 H), 1.24 (t, 3 H).

Hydrolysis of **16e** (2.73 g, 6.32 mmol) afforded **17e** (1.53 g, 62%) as a light yellow solid. IR (KBr): ν_{max} 3371, 1691, 1694, 1612, 1558, 1215 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.76 (bs, 2 H), 12.12 (s, 1 H), 8.02 (s, 1 H), 7.32 (d, 1 H, J = 1.8 Hz), 7.14 (d, 1 H, J = 1.8 Hz), 6.89 (d, 2 H J = 8.5 Hz), 6.85 (d, 2 H, J = 8.5 Hz), 2.15 (s, 3 H). MS: *m/z* 389 (M^+ − 1), 372 (M^+ − 18), 344, 115. Anal. $C_{19}H_{13}Cl_2NO_4 \cdot H_2O$: C, H, N.

3-[2-Carboxy-2-(4-(trifluoromethyl)phenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17f from 15f via 16f. (4-(Trifluoromethyl)phenyl)acetic acid methyl ester (**14f**) was prepared according to a literature procedure.[31] The spectra agreed with the published spectra.

Compound **14f** (7.87 g, 36.1 mmol) was treated as described in general procedure II to afford **15f** (7.27 g, 77%) as a yellow oil. IR (KBr): ν_{max} 1740, 1713, 1632, 1620, 1437, 1327, 1279, 1262, 1194, 1165 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1 H), 7.59 (d, 2 H, J = 8.2 Hz), 7.47 (d, 2 H, J = 8.2 Hz), 3.87 (s, 3 H), 3.75 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 160.4, 130.5, 127.9, 124.6 (q, J = 3.8 Hz), 62.2, 51.6. ^{19}F NMR ($CDCl_3$): δ −63.1 Hz. MS: *m/z* 521 ($2M^+$ + 1), 289 (M^+ + 29), 261 (M^+ + 1), 257, 241, 229 (100), 213, 173, 75.

Compound **15f** (5.62 g, 21.6 mmol) was then reacted with indole **5** (5.07 g, 19.6 mmol) to afford **16f** (5.07 g, 53%) as a tan powder. IR (KBr): ν_{max} 3304, 1717, 1705, 1682, 1325, 1298, 1244, 1169, 1126, 1111, 1069 cm^{-1}. MS: *m/z* 514 (M^+ + 29), 486 (M^+ + 1), 466, 454 (100).

Hydrolysis (vide supra) of diester **16f** (5.0 g, 10 mmol), followed by recrystallization from EtOAc and acetone/cyclohexane, gave **17f** (1.46 g, 34%) as an ivory powder. IR (KBr): ν_{max} 3096, 1692, 1615, 1327, 1244, 1219, 1171, 1130, 1111, 1069 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.13 (bs, 1 H), 12.22 (s, 1 H), 8.20 (s, 1 H), 7.5 (m, 2 H), 7.35 (d, 1 H, J = 1.3 Hz), 7.2 (m, 3 H)—acetone present. ^{13}C NMR (DMSO-d_6): δ 167.2, 161.4, 140.2, 136.9, 135.5, 134.9, 130.6, 128.9, 127.4, 127.0, 125.9, 124.03 124.0, 122.4, 122.3, 121.0, 114.7, 111.3. ^{19}F NMR (DMSO-d_6): δ −60.6 (s). MS: *m/z* 443 (M^+ + 1), 426 (100). Anal. $C_{19}H_{10}F_3Cl_2NO_4$: C, H, N.

3-[2-Carboxy-2-(3-nitrophenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17g from 15g via 16g. Methyl ester **14g** (21.5 g, 100%) was prepared from *m*-nitrophenylacetic acid (20.0 g, 110 mmol) as a white solid and was used without further purification. The NMR agreed with published data. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1 H, J = 1.1 Hz), 8.14 (dd, 1 H, J = 7.7, 1.0 Hz), 7.63 (dd, 1 H, J = 7.7, 1.1 Hz), 7.52 (t, 1 H, J = 7.7 Hz), 3.75 (s, 2 H), 3.73 (s, 3 H).

Methyl *m*-nitrophenylacetate (**14g**; 15.3 g, 78.3 mmol) was treated as described in general procedure II to afford enol ether **15g** (13.9 g, 75%) as a yellow solid: mp 101−103 °C.

This was reacted with indole **5** (11.7 g, 45.2 mmol) to afford *m*-nitro diester **16g** (13.0 g, 62%) as a yellow solid: TLC, cyclohexane/EtOAc (7:3), R_f = 0.5. IR (KBr): ν_{max} 1721, 1686, 1532, 1350, 1323, 1242 cm^{-1}. MS: *m/z* 463 (M^+ + 1), 462, 433 (M^+), 433, 431, 417, 371, 238, 210. The isomers can be separated by fractional recrystallization from EtOAc/cyclohexane. The *Z* isomer of **16g** precipitates as a yellow powder, which can then be recrystallized from Et_2O/cyclohexane to obtain pure *Z* isomer of **16g** as yellow needles: mp 178−180 °C. IR (KBr): ν_{max} 3408, 3316, 1715, 1530, 1443, 1350, 1319, 1238, 1209, 1182 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.46 (bs, 1 H), 8.27 (t, 1 H, J = 1.9 Hz), 8.22 (dm, 1 H, J = 8.2 Hz), 7.92 (dm, 1 H, J = 8.0 Hz), 7.71 (t, 1 H, J = 8.0 Hz), 7.60 (s, 1 H), 7.44 (d, 1 H, J = 1.7 Hz), 7.17 (d, 1 H, J = 1.7 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 3.41 (s, 3 H), 1.23 (t, 3 H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6): δ 166.0, 160.6, 147.7, 139.6, 137.1, 134.5, 133.8, 133.8, 129.9, 129.1, 127.3, 125.6, 122.7, 122.4, 122.0, 121.2, 116.4, 111.4, 61.1, 51.6, 13.9. MS: *m/z* 491 (M^+ + 29), 462 (M^+), 431 (100). Anal. $C_{21}H_{16}Cl_2N_2O_6$: C, H, N. The pure *E* isomer of **16g** was isolated as an ivory powder: mp 173−175 °C. IR (KBr): ν_{max} 3399, 3304, 1715, 1556, 1532, 1437, 1350, 1321, 1300, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.35 (bs, 1 H), 8.25 (s, 1 H), 7.96 (dm, 1 H, J = 7.6 Hz), 7.86 (m, 1 H), 7.39 (t, 1 H, J = 7.6 Hz), 7.36 (dm, 1 H, J = 7.6 Hz), 7.33 (d, 1 H, J = 1.7 Hz), 7.14 (d, 1 H, J = 1.7 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.81 (s, 3 H), 1.23 (t, 3 H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6): δ 165.8, 159.8, 146.8, 137.1, 136.7, 136.3, 136.0, 133.7, 129.4, 129.1, 126.9, 125.7, 124.5, 122.2, 122.1, 121.3, 114.7, 111.4, 61.1, 52.5, 13.2. MS: *m/z* 491 (M^+ + 29), 462 (M^+), 431 (100). Anal. $C_{21}H_{16}Cl_2N_2O_6$: C, H, N.

Hydrolysis (vide supra) of the *m*-nitro diester **16g** (876 mg, 1.89 mmol) in THF (8 mL) and H_2O (4 mL) with LiOH (272 mg, 11.3 mmol) at 70 °C for 16 h provided, after recrystallization from EtOAc, diacid **17g** (354 mg, 44%) of as a light yellow powder: mp 272−275 °C. IR (KBr): ν_{max} 3414, 3298, 1691, 1612, 1530, 1350, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.20 (bs, 1 H), 12.28 (s, 1 H), 8.27 (s, 1 H), 7.95−8.00 (m, 1 H), 7.85−7.90 (m, 1 H), 7.30−7.45 (m, 3 H), 7.19 (s, 1 H). MS: *m/z* 420 (M^+), 403 ($M^+ - H_2O$), 377, 258, 230, 195. Anal. $C_{18}H_{10}Cl_2N_2O_6 \cdot H_2O$: C, H, N.

(*E*)-3-[2-Carboxy-2-(2-chlorophenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 17h from 15h via 16h. (2-Chlorophenyl)acetic acid methyl ester (**14h**; 4.1 g, 22 mmol) was treated as described in general procedure II to afford the crude enol ether **15h** (2.85 g, 56%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.57 (s, 1 H), 7.39−7.43 (m, 1 H), 7.21−7.26 (m, 3 H), 3.83 (s, 3 H), 3.70 (s, 3 H).

The crude enol ether **15h** (2.8 g, 12 mmol) was treated (vide supra) to afford diester **16h** (1.3 g, 27%) as a white solid: mp

201−206 °C. IR (KBr): ν_{max} 3420, 3410, 3304, 3084, 3024, 2987, 2951, 2904, 1724, 1705, 1678, 1641, 1612, 1558, 1533, 1473, 1435, 1390, 1369, 1323, 1292, 1242, 1197 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.99 (bs, 1 H), 8.32 (s, 1 H), 6.96−7.32 (m, 6 H), 4.35 (q, 2 H, J = 7.4 Hz), 3.88 (s, 3 H), 1.37 (t, 3 H, J = 7.1 Hz). MS: *m/z* 482 (M^+ + 29), 452 (M^+ + 1), 420 (M^+ + 1 − MeOH, 100). Anal. $C_{21}H_{16}Cl_3NO_4$: C, H, N.

Hydrolysis of **16h** (1.3 g, 2.9 mmol) gave diacid **17h** (0.9 g, 90%) as a pale yellow solid: mp 244−246 °C (dec). IR (KBr): ν_{max} 3423, 3259, 3161, 3090, 2692, 2681, 2671, 2656, 2613, 2604, 2542, 1695, 1633, 1614, 1558, 1533, 1473, 1438, 1411, 1392, 1369, 1338 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.7 (bs, 1.2 H), 12.17 (s, 1 H), 8.16 (s, 1 H), 6.99−7.33 (overlapping m, 6 H). ^{13}C NMR (DMSO-d_6): δ 167.2, 161.6, 136.7, 135.1, 134.8, 134.6, 133.3, 131.7, 128.9, 128.8, 128.7, 127.2, 127.1, 125.9, 122.6, 120.8, 114.5, 111.2. MS: *m/z* 438 (M^+ + 29), 410 (M^+ + 1). Anal. $C_{18}H_{10}Cl_3NO_4 \cdot 0.5C_3H_6O$: C, H, N.

3-[2-(3-Aminophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 19 from 18. To a solution of *m*-nitro ester **16g** (16.2 g, 34.9 mmol) in EtOAc (175 mL) was added $SnCl_2 \cdot 2H_2O$ (47.2 g, 209 mmol). The mixture was heated to reflux for 4 h and then allowed to cool to rt, neutralized with saturated $NaHCO_3$, and diluted with H_2O and EtOAc; the emulsion was allowed to dissipate, and the aqueous phase separated. The aqueous phase was extracted with EtOAc (3×), and the combined organic phases were washed with brine and dried ($MgSO_4$). The crude product was purified by flash chromatography (2:1 hexane/EtOAc) to afford amino diester **18** (13.9 g, 92%) as a light yellow solid: mp 249−251 °C. IR (KBr): ν_{max} 3402, 3379, 3327, 1709, 1609, 1321, 1238 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.36 (s, 1 H), 7.45 (d, 1 H, J = 1.7 Hz), 7.32 (s, 1 H), 7.22 (d, 1 H, J = 1.7 Hz), 7.05 (t, 1 H, J = 7.8 Hz), 6.67 (d, 1 H, J = 1.9 Hz), 6.55−6.62 (m, 2 H), 5.16 (s, 1 H), 4.27 (q, 2 H, J = 7.1 Hz), 3.39 (s, 3 H), 1.25 (t, 3 H, J = 7.1). MS: *m/z* 433 (M^+), 432 (M^+ − 1), 403, 401, 359, 327, 300. Anal. $C_{21}H_{18}Cl_2N_2O_4 \cdot 0.5H_2O$: C, H, N.

To *m*-amino ester **18** (550 mg, 1.27 mmol) in THF (7 mL) and H_2O (5 mL) was added LiOH (304 mg, 12.7 mmol). The mixture was heated to 70 °C for 24 h. The mixture was allowed to cool, the THF removed in vacuo, and the aqueous phase washed with EtOAc. The aqueous phase was filtered through Celite, acidified with aqueous $NaHSO_4$ to pH 4, and extracted three times with EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$). The crude product was recrystallized from EtOAc. The recrystallized material was dissolved in hot MeOH, filtered through Celite, and precipitated by the addition of H_2O. The precipitate was filtered through a fritted disk, dried first under a stream of N_2, and then dried in vacuo at 80 °C overnight to afford **19** (310 mg, 62%) as a light yellow powder: mp 211−220 °C. IR (KBr): ν_{max} 3430, 3246, 1694, 1611, 1240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.1 (s, 1 H), 7.93 (s, 1 H), 7.31 (d, 1 H, J = 1.6 Hz), 7.12 (d, 1 H, J = 1.1 Hz), 6.67 (t, 1 H, J = 7.6 Hz), 6.27 (s, 1 H), 6.24 (d, 1 H, J = 1.1 Hz), 6.10 (d, 1 H, J = 7.6 Hz). MS: *m/z* 391 (M^+), 373 (M^+ − 18), 347, 345, 329, 99. Anal. $C_{18}H_{12}Cl_2N_2O_4 \cdot 0.58H_2O$: C, H, N.

3-[2-(3-(Acetylamino)phenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 21a from 18 via 20a. To a solution of the *m*-amino diester **18** (2.0 g, 4.6 mmol) in CH_2Cl_2 (45 mL) was added Et_3N (1.9 mL, 14 mmol) and CH_3COCl (0.82 mL, 12 mmol). The mixture was allowed to stir at rt for 20 h. The reaction was quenched by addition of MeOH and the mixture diluted with CH_2Cl_2. The organic phase was washed with brine and dried ($MgSO_4$). The crude product **20a** was used without further purification.

Hydrolysis (vide supra) of the *N*-acetyl ester **20a** (2.39 g, 4.62 mmol) in THF (25 mL) and H_2O (20 mL) with LiOH (664 mg, 27.7 mmol) at 70 °C for 16 h gave **21a** (1.74 g, 87%) as a light yellow powder: mp 270−271 °C (dec). IR (KBr): ν_{max} 3414, 3279, 1688, 1613, 1557, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.14 (s, 1 H), 9.73 (s, 1 H), 8.03 (s, 1 H), 7.39 (dd, 1 H, J = 2.0, 7.7 Hz), 7.31 (d, 1 H, J = 1.5 Hz), 7.24 (d, 1 H, J = 2.0 Hz), 7.13 (d, 1 H, J = 1.5 Hz), 6.94 (t, 1 H, J = 7.7 Hz), 6.57 (dd, 1 H, J = 1.0, 7.7 Hz), 1.94 (s, 3 H). MS: *m/z* 432 (M^+ − 1), 415 (M^+ − 18), 387, 373, 326, 235, 176, 123. Anal. $C_{20}H_{14}Cl_2N_2O_5 \cdot 0.5HOAc \cdot 0.5EtOAc$: C, H, N.

3-[2-(3-(Benzoylamino)phenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 21b from 18 via 20b. The benzamide diester **20b** was prepared (vide supra) from *m*-amino diester **18** (866 mg, 2.0 mmol) and PhCOCl (0.58 mL, 5.0 mmol). The crude product was used without further purification.

Hydrolysis of the benzamide diester **20b** (920 mg, 1.43 mmol) gave, after crystallization from EtOAc/hexane, **21b** (350 mg, 56%) as a yellow powder: mp 237−238 °C (dec). IR (KBr): ν_{max} 3420, 3275, 1686, 1611, 1537, 1234 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.16 (s, 1 H), 10.07 (s, 1 H), 8.06 (s, 1 H), 7.85−7.95 (m, 2 H), 7.45−7.60 (m, 4 H), 7.31 (d, 1 H, J = 1.8 Hz), 7.13 (d, 1 H, J = 1.8 Hz), 6.94 (t, 1 H, J = 7.7 Hz), 6.65 (dd, 1 H, J = 1.0, 7.7 Hz). MS: *m/z* 495 (M^+), 256, 151. Anal. ($C_{25}H_{16}Cl_2N_2O_5$) C, H, N.

3-[2-Carboxy-2-(3-(methoxycarbonylamino)phenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 21c from 18 via 20c. Diester **18** (1.19 g, 2.74 mmol) was treated with $ClCO_2Me$ (0.25 mL, 3.3 mmol) to afford the pure *E* isomer of **20c** (0.69 g, 51%) as a white powder: mp 192−194 °C. IR (KBr): ν_{max} 3293, 1742, 1705, 1611, 1553, 1441, 1321, 1300, 1285, 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.61 (bs, 1 H), 8.16 (s, 1 H), 7.25 (d, 1 H, J = 1.7 Hz), 7.19 (bs, 1 H), 7.04 (bs, 1 H), 7.01 (d, 1 H, J = 1.7 Hz), 6.93 (t, 1 H, J = 1.7 Hz), 6.64 (d, 1 H, J = 7.6 Hz), 4.21 (q, 2 H, J = 7.1 Hz), 3.79 (s, 3 H), 3.64 (s, 3 H), 2.19 (bs, 1 H), 1.28 (t, 3 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 167.3, 160.8, 153.8, 137.3, 137.0, 136.0, 135.9, 134.6, 130.4, 128.0, 127.8, 125.1, 124.6, 123.2, 121.8, 112.0, 117.4, 116.4, 110.9, 61.1, 52.2, 51.9, 14.1. MS: *m/z* 519 (M^+ + 29), 490 (M^+), 459 (100). Anal. $C_{23}H_{20}Cl_2N_2O_6$: C, H, N. Flash chromatograhy (2:1 cyclohexane/EtOAc) of the filtrate gave an ∼1:1 mixture of *E* and *Z* isomers **20c** (0.52 g, 39%) as a pale yellow powder: mp 87−92 °C. IR (KBr): ν_{max} 3337, 1705, 1611, 1555, 1545, 1443, 1319, 1300, 1283, 1238 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.34 (bs, 1 H), 9.15 (bs, 1 H), 8.20 (s, 1 H), 7.53 (bt, 1 H, J = 1.7 Hz), 7.44 (m, 1 H), 7.43 (s, 1 H), 7.34 (t, 1 H, J = 8.0 Hz), 7.21 (dt, 1 H, J = 7.6, 1.4 Hz), 7.18 and 7.16 (2d, 3 H, J = 1.7 Hz), 7.10 (d, 2 H, J = 1.7 Hz), 7.08 (bt, 1 H, J = 1.7 Hz), 7.00 (t, 1 H, J = 8.0 Hz), 6.76 (bs, 1 H), 6.73 (dt, 1 H, J = 7.7, 1.3 Hz), 6.50 (bs, 1 H), 4.33 (q, 2 H, J = 7.1 Hz), 4.28 (q, 2 H, J = 7.1 Hz), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.56 (bs, 3 H), 1.34 (t, 3 H, J = 7.1 Hz), 1.31 (t, 3 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 167.5, 167.3, 161.4, 160.7, 159.3, 154.0, 139.3, 137.8, 137.0, 136.8, 136.6, 136.5, 136.5, 136.0, 134.4, 131.9, 131.2, 131.0, 128.9, 128.7, 128.5, 128.1, 124.9, 124.8, 123.5, 123.4, 122.9, 122.4, 122.4, 118.3, 118.1, 117.8, 117.1, 110.6, 110.5, 61.6, 52.4, 52.2, 51.7, 14.2, 14.1. MS: *m/z* 519 (M^+ + 29), 490 (M^+), 459 (100), 234.

Hydrolysis of the diester **20c** (1.11 g, 2.26 mmol) provided **21c** (279 mg, 28%) as an ivory powder: mp 250 °C (dec). IR (KBr): ν_{max} 3372, 3081, 1688, 1609, 1589, 1539, 1443, 1294, 1240, 1175 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.86 (bs, 2 H), 12.10 (s, 1 H), 9.43 (s, 1 H), 8.05 (s, 1 H), 7.32 (d, 1 H, J = 1.8 Hz), 7.2 (m, 2 H), 7.12 (d, 1 H, J = 1.8 Hz), 6.96 (t, 1 H, J = 7.9 Hz), 6.59 (dt, 1 H, J = 7.7, 1.3 Hz), 3.59 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ 167.9, 161.7, 153.7, 138.0, 136.8, 136.6, 136.4, 133.7, 128.5, 127.2, 127.1, 123.8, 122.3, 120.6, 119.8, 116.6, 115.2, 111.0, 51.4. MS: *m/z* 477 (M^+ + 29), 459, 448 (M^+), 431 (100), 399, 387. Anal. $C_{20}H_{14}Cl_2N_2O_6$: C, H, N.

3-[2-Carboxy-2-(3-(methanesulfonylamino)phenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 21d from 18 via 20d. Diester **18** (1.12 g, 2.58 mmol) was reacted with $MeSO_2Cl$ (0.24 mL, 3.1 mmol) to afford **20d** (1.19 g, 90%) as a yellow amorphous solid. IR (KBr): ν_{max} 3410, 3297, 1703, 1609, 1437, 1321, 1240, 1152, 980 cm^{-1}. ^{1}H NMR ($CDCl_3$); *E* isomer: δ 9.37 (bs, 1 H), 8.24 (s, 1 H), 7.22 (d, 1 H, J = 1.7 Hz), 7.07 (d, 1 H, J = 1.7 Hz), 6.9−7.0 (m, 4 H), 6.65 (bs, 1 H), 4.31 (q, 2 H, J = 7.2 Hz), 3.87 (s, 3 H), 2.60 (s, 3 H), 1.36 (t, 3 H, J = 7.2 Hz). ^{1}H NMR ($CDCl_3$); *Z* isomer: 9.32 (bs, 1 H), 7.48 (s, 1 H), 7.3−7.4 (m, 4 H), 7.25 (d, 1 H, J = 1.7 Hz), 7.12 (d, 1 H, J = 1.7 Hz), 7.10 (m, 1 H), 4.35 (q, 2 H, J = 7.2 Hz), 3.53 (s, 3 H), 3.06 (s, 3 H), 1.32 (t, 3 H, J = 7.2 Hz). ^{13}C NMR

($CDCl_3$): δ 167.2, 167.0, 161.3, 160.9, 140.0, 136.8, 136.7, 136.7, 136.6, 136.1, 136.0, 135.8, 134.9, 132.4, 131.3, 131.2, 129.6, 128.7, 128.5, 127.2, 125.2, 125.0, 124.9, 123.1, 122.6, 122.5, 122.2, 120.4, 120.1, 119.9, 118.1, 117.0, 110.7, 110.6, 61.8, 61.7, 52.5, 51.8, 39.4, 38.6, 21.0, 14.2. MS: *m/z* 511 ($M^+ + 1$), 510 (M^+), 479, 203, 186 (100), 160.

Hydrolysis of the diester **20d** (1.17 g, 2.29 mmol) provided **21d** (0.50 g, 47%) as an ivory powder: mp > 270 °C. IR (KBr): ν_{max} 3418, 3300, 3200, 3094, 1686, 1615, 1319, 1306, 1240, 1140, 980 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.93 (bs, 2 H), 12.18 (s, 1 H), 9.44 (s, 1 H), 8.07 (s, 1 H), 7.32 (d, 1 H, J = 1.7 Hz), 7.13 (d, 1 H, J = 1.7 Hz), 7.08 (dt, 1 H, J = 7.7, 0.7 Hz), 6.9 (m, 2 H), 6.80 (dm, 1 H, J = 7.7 Hz), 2.48 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ 167.6, 161.5, 137.1, 136.9, 136.8, 136.4, 134.0, 128.7, 127.9, 127.1, 126.9, 125.9, 122.2, 121.3, 120.8, 118.9, 115.4, 111.1, 38.0. MS: *m/z* 479, 468 (M^+), 451 (100), 266, 186. Anal. $C_{19}H_{14}Cl_2N_2O_6S$: C, H, N.

3-[2-Carboxy-2-(3-(dimethylamino)phenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 21e from 18 via 20e. To a solution of the *m*-amino diester **18** (1.08 g, 2.5 mmol) in AcOH (15 mL) was added paraformaldehyde (751 mg, 25.0 mmol) followed by $NaBH_3CN$ (786 mg, 12.5 mmol), and the mixture was stirred at rt for 20 h. The mixture was then adjusted to pH < 9 with 1 M NaOH solution, extracted with EtOAc, and the organic phases washed with brine and dried ($MgSO_4$), affording after flash chromatography (2:1 hexane/EtOAc) dimethylamino diester **20e** (970 mg, 84%) as a light yellow powder. ^1H NMR (DMSO-d_6): δ 12.24 (s, 1 H), 7.99 (s, 1 H), 7.34 (d, 1 H, J = 1.6 Hz), 7.20 (d, 1 H, J = 1.6 Hz), 6.92 (t, 1 H, J = 8.5 Hz), 6.43 (dd, 1 H, J = 8.5, 1.1 Hz), 6.30 (d, 1 H, J = 8.5 Hz), 6.24 (d, 1 H, J = 1.1 Hz), 4.20 (q, 2 H, J = 7.4 Hz), 3.75 (s, 3 H), 2.58 (s, 6 H), 1.25 (t, 3 H, J = 7.4 Hz).

Hydrolysis of **20e** (970 mg, 2.10 mmol) provided, after crystallization from EtOAc/hexane, **21e** (494 mg, 56%) as a light yellow powder: mp 256−258 °C. IR (KBr): ν_{max} 3425, 1692, 1602, 1557, 1240 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.10 (s, 1 H), 7.99 (s, 1 H), 7.32 (d, 1 H, J = 1.6 Hz), 7.14 (d, 1 H, J = 1.6 Hz), 6.91 (t, 1 H, J = 7.7 Hz), 6.25−6.45 (m, 3 H), 2.62 (s, 6 H). MS: *m/z* 419 (M^+), 401 ($M^+ - 18$), 383, 329, 271, 178. Anal. $C_{20}H_{14}Cl_2N_2O_5 \cdot 0.5H_2O \cdot 0.5$EtOAc: C, H, N.

3-[2-Carboxy-2-(3-(methylamino)phenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 21f from 18 via 20f. A mixture of *m*-amino diester **18** (5.45 g, 12.6 mmol) and HCO_2Et (800 mL) was allowed to stir at rt overnight. By the next day all the solids had dissolved. The HCO_2Et was removed in vacuo, and the residue was taken up in EtOAc, washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). The crude formamide was dissolved in THF (50 mL), and $BH_3 \cdot SMe_2$ complex (15 mL of a 2 M solution in THF) was added. The resulting solution was heated to 60 °C for 15 min, then cooled to rt, quenched with MeOH, and stirred for 2 h. The crude material was chromatographed (7:3 cyclohexane/EtOAc) to afford **20f** (2.5 g, 44% of a ~6:1 mixture of *E*/*Z* isomers) as a yellow powder. IR (KBr): ν_{max} 3410, 3306, 1707, 1680, 1607, 1559, 1441, 1321, 1296, 1244 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.28 and 9.12 (major) (bs, 1 H), 8.13 (major) and 7.52 (s, 1 H), 7.23 (t, 1 minor H, J = 7.8 Hz), 7.09 (d, 1 major H, J = 1.7 Hz), 7.01 (d, 1 major H, J = 1.7 Hz), 6.9 (m, 1 major + 1 minor H), 6.86 (m, 1 minor H), 6.62 (m, 1 minor H), 6.46 (m, 1 major H), 6.3 (m, 2 major + 1 minor H), 4.34 and 4.28 (major) (q, 2 H, J = 7.2 Hz), 3.85 (major) and 3.58 (s, 3 H), 2.88 and 2.55 (major) (s, 3 H), 1.35 (major) and 1.34 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ (major peaks) 167.7, 161.0, 148.3, 137.5, 136.5, 136.1, 133.8, 131.0, 128.5, 128.2, 124.6, 123.7, 122.2, 118.9, 117.5, 113.8, 111.9, 110.9, 61.4, 52.3, 30.4, 14.1. MS: *m/z* 475 ($M^+ + 29$), 447 ($M^+ + 1$, 100), 415, 373, 341.

Hydrolysis of diester **20f** (1.9 g, 4.2 mmol) gave **21f** (0.70 g, 41%, a ~6:1 mixture of *E*/*Z* isomers) as an ivory powder: mp 193 °C (dec). IR (KBr): ν_{max} 3426, 1694, 1609, 1557, 1535, 1437, 1414, 1366, 1331, 1236 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.25 and 12.07 (major) (2s, 1 H), 7.93 (major) and 7.39 (2s, 1 H), 7.42 and 7.30 (major) (2d, 1 H, J = 1.7 Hz), 7.18 and 7.12 (major) (2d, 1 H, J = 1.7 Hz), 7.09 (m, 1 minor H), 6.76 (t, 1 major H, J = 7.8 Hz), 6.6−6.7 (m, 2 minor H), 6.51 (m, 1 minor H), 6.2 (m, 3 major H), 2.67 and 2.38 (major) (2s, 3 H). ^{13}C NMR (DMSO-d_6): δ (major peaks) 168.1, 161.8, 148.6, 137.8, 136.9, 136.3, 133.0, 128.6, 127.4, 126.6, 122.6, 120.6, 117.1, 116.1, 112.7, 111.1, 110.8, 29.4. MS: *m/z* 433 ($M^+ + 29$), 405 ($M^+ + 1$, 100), 387, 361, 123. Anal. $C_{19}H_{14}Cl_2N_2O_4 \cdot 0.91H_2O$: C, H, N.

3-[2-(4-Aminophenyl)-2-cyanovinyl]-4,6-dichloro-1*H*-indole-2-carboxylic acid, 26a from 6 via 25a. To the aldehyde **6** (858 mg, 3.0 mmol) in EtOH (45 mL) was added (*p*-nitrophenyl)acetonitrile (584 mg, 3.6 mmol) and piperidine (30 μL, 0.3 mmol). The mixture was refluxed for 18 h and cooled to rt. The precipitate was filtered and washed with EtOH and dried to afford **25a** (1.18 g, 91%) as a bright yellow solid. IR (KBr): ν_{max} 3402, 3283, 2224, 1709, 1684, 1609, 1522, 1344, 1238 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.92 (s, 1 H), 8.65 (s, 1 H), 8.36 (d, 1 H, J = 8.9 Hz), 8.03 (d, 1 H, J = 8.9 Hz), 7.53 (d, 1 H, J = 1.6 Hz), 7.37 (d, 1 H, J = 1.6 Hz), 4.34 (q, 2 H, J = 7.1 Hz), 1.24 (t, 3 H, J = 7.1). MS: *m/z* 430 ($M^+ + 1$), 412, 387, 384 ($M^+ -$ EtOH). Anal. $C_{20}H_{13}Cl_2N_3O_4$: C, H, N.

Reduction of the *p*-nitro ester **25a** (6.93 g, 16.1 mmol) in EtOH (50 mL) with $SnCl_2 \cdot 2H_2O$ (18.2 g, 80.5 mmol) yielded, after flash chromatography (2:1 hexane/EtOAc), *p*-amino ester **25b** (6.20 g, 96%) as a bright yellow solid. IR (KBr): ν_{max} 3385, 3302, 2222, 1690, 1622, 1609, 1514, 1238 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.15 (s, 1 H), 7.85 (s, 1 H), 7.52 (d, 1 H, J = 7.4 Hz), 7.31 (s, 1 H), 7.14 (d, 1 H, J = 1.3 Hz), 6.74 (d, 1 H, J = 7.4 Hz), 4.36 (q, 2 H, J = 7.1 Hz), 1.27 (t, 3 H, J = 7.1). MS: *m/z* 400 ($M^+ + H$), 399 (M^+), 354 ($M^+ -$ EtOH), 325, 290. Anal. $C_{20}H_{15}Cl_2N_3O_2$: C, H, N.

Hydrolysis of the *p*-amino ester **25b** (970 mg, 2.10 mmol) afforded, after crystallization from EtOAc/hexane, nitrile acid **26a** (494 mg, 56%) as a light yellow powder. IR (KBr): ν_{max} 3387, 3285, 2224, 1695, 1610, 1558, 1514, 1235 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.54 (s, 1 H), 7.88 (s, 1 H), 7.47 (d, 1 H, J = 1.7 Hz), 7.40 (d, 1 H, J = 8.5 Hz), 7.27 (d, 1 H, J = 1.7 Hz), 6.66 (d, 1 H, J = 8.5 Hz). MS: *m/z* 372 (M^+), 371 ($M^+ - 1$), 336, 328, 285. Anal. $C_{18}H_{11}Cl_2N_3O_2$: C, H, N.

3-[2-(4-Aminophenyl)-2-carboxyvinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 26b. To the *p*-amino ester **25b** (6.20 g, 15.5 mmol) was added AcOH (20 mL) and H_2SO_4 (20 mL). The reaction mixture was heated to 70 °C and stirred for 3 h. The reaction mixture was cooled in an ice bath and the resulting precipitate collected by filtration and dried in vacuo affording the intermediate amide ester (3.0 g, 45%) as a brown solid. ^1H NMR (DMSO-d_6): δ 12.24,12.20 (s, 1 H), 7.64 (s, 1 H), 7.40 (m, 2 H), 7.2 (s, 2 H), 6.84 (d, 2 H), 6.80 (d, 2 H), 4.20 (q, 2 H), 3.4−4.4 (bs, 2 H), 1.25 (t, 3 H). To the amide ester (1.90 g, 5.38 mmol) was added 6 N NaOH (20 mL), and the mixture was heated to 105 °C for 14 h. The mixture was then cooled to 0 °C, acidified to pH 3 with 6 N HCl, and the resulting precipitate collected by filtration and dried in vacuo to afford **26b** (1.34 g, 66%) as a brown solid. IR (KBr): ν_{max} 3395, 3271, 1724, 1612, 1176, 1082 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.12 (s, 1 H), 7.87 (s, 1 H), 7.33 (d, 1 H, J = 1.8 Hz), 7.10 (d, 1 H, J = 1.8 Hz), 6.62 (d, 2 H, J = 8.6 Hz), 6.23 (d, 2 H, J = 8.6 Hz). MS: *m/z* 392 ($M^+ + 1$), 390 ($M^+ - 1$), 354, 348, 346, 310. Anal. $C_{18}H_{12}Cl_2N_2O_4$: C, H, N.

General Procedure III for the Mukaiyama Condensation of Ketene Silyl Acetals with 6. The ketene silyl acetals **28a**−**g** of the arylalkylesters **27a**−**g** were generated by treating the esters (29.3 mmol) at 0 °C, under N_2, with a cold solution of TMSOTf (99%, 6.33 mL, 33.0 mmol) and Et_3N (4.6 mL, 33.0 mmol) in anhydrous Et_2O (60 mL), dropwise over 10 min. After stirring the reaction for 4 h, the reaction was allowed to gradually warm to rt, at which time the colorless reaction acquired a yellow denser layer. This was separated from the Et_2O layer, and the Et_2O layer was concentrated to a colorless oil. In a separate reaction vessel Ph_3PO (1.3 g, 4.68 mmol) was cooled to 0 °C under N_2 in CH_2Cl_2. A solution of Tf_2O (0.40 mL, 2.34 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 5 min. After 10 min this solution was added dropwise over 5 min to a stirred suspension of the freshly prepared ketene silyl acetal and **6** (3.7 g, 12.85 mmol) in CH_2Cl_2 at −78 °C. The reaction was stirred at −78 °C for 1 h

during which time a white solid started to precipitate. The reaction was allowed to gradually warm to rt overnight. After 16 h the reaction was poured on H_2O and extracted with EtOAc, washed with saturated $NaHCO_3$ followed by brine, dried ($MgSO_4$), and concentrated to an amber oil which solidified upon standing. Recrystallization from hot Et_2O/$CHCl_2$ afforded pure product.

4,6-Dichloro-3-(2-(methoxycarbonyl)-2-phenylvinyl)-1*H*-indole-2carboxylic Acid Ethyl Ester, 31a from 27a via 29a/30a. Methyl phenylacetate **27a** (1.80 mL, 12.5 mmol) was treated as described in general procedure III and reacted with aldehyde **6** (1.57 g, 5.49 mmol) to afford **29a** (85:15 mixture of two diastereomers, 333 mg, 12%,) and **30a** (253 mg of less polar diastereomer A, 623 mg of diastereomeric mixture, and 407 mg of more polar diastereomer B; total 1.283 g, 54%), all as white solids. The TMS ethers **29a** were recrystallized from cyclohexane to give fine white crystals: mp 150−153 °C. IR (KBr): ν_{max} 3329, 1730, 1688, 1238, 1167, 1080, 843 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.01 and 8.68 (major) (two s, 1 H), 7.28 (major) and 7.14 (two d, 1 H, J = 1.8 Hz), 7.2−7.25 (m, 2 H of minor) and 6.95−7.07 (m, 5 H of major and 3 H of minor), 7.18 (major) and 7.14 (two d, 1 H, J = 1.8 Hz), 6.76 and 6.62 (major) (two d, 1 H, J = 10.1 and 10.5 Hz), 4.93 and 4.72 (major) (two d, 1 H, J = 10.1 and 10.5 Hz), 4.54 (q, J = 7.1 Hz; 2H of minor), 4.39 and 4.30 (two dq, J = 10.8, 7.1 Hz, 2H of major), 3.75 (major) and 3.74 (two s, 3 H), 1.53 and 1.47 (major) (two t, 3 H, J = 7.1 Hz), −0.05 (major) and −0.07 (two s, 9 H). MS: *m/z* 536 (M^+ + 29), 510, 508 (M^+ + 1), 494, 492, 420, 418, 388, 386, 360, 358 (100). Anal. $C_{24}H_{27}Cl_3NO_5Si$: C, H, N. The diastereomerically pure fractions of alcohols **30a** were individually recrystallized from cyclohexane/EtOAc. Alcohol **30a** (diastereomer A) was obtained as fine white needles: mp 206−208 °C (change at 170 °C). IR (KBr): ν_{max} 1740, 1686, 1246 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.24 (bs, 1 H), 7.49 (d, 1 H, J = 1.8 Hz), 7.25−7.48 (m, 5 H), 7.29 (d, 1 H, J = 1.8 Hz), 6.44 (dd, 1 H, J = 9.9, 7.1 Hz), 5.24 (d, 1 H, J = 7.1 Hz), 4.56 (bs, 1 H), 4.43 (q, 2 H, J = 7.1 Hz), 3.18 (s, 3 H), 1.43 (t, 3 H, J = 7.1 Hz). MS: *m/z* 438, 436 (M^+ + 1), 420, 418, 388, 386, 288, 286 (100). Anal. $C_{21}H_{19}Cl_2NO_5$: C, H, N. Aldol **30a** (diastereomer B) was isolated as white granules: mp 177−178 °C. IR (KBr): ν_{max} 1736, 1723, 1686, 1310, 1244, 1167 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.99 (bs, 1 H), 7.10−7.15 (m, 3 H), 6.97−7.03 (m, 4 H), 6.64 (dd, 1 H, J = 11.2, 10.1 Hz), 5.30 (bs, 1 H), 4.50 (q, 2 H, J = 7.1 Hz), 4.38 (bd, 1 H), 3.78 (s, 3 H), 1.49 (t, 3 H, J = 7.1 Hz)—trace cyclohexane and EtOAc present. MS: *m/z* 438, 436 (M^+ + 1), 420, 418, 388, 386, 288, 286 (100). Anal. $C_{21}H_{19}Cl_2NO_5$: C, H, N.

To a stirred solution of alcohols **30a** (diastereomeric mixture, 232 mg, 0.532 mmol) in toluene (25 mL) at 65 °C under N_2 was added *p*-TsOH (10 mg). The solution was heated at gentle reflux for 2.5 h and then allowed to cool to rt before being washed twice with H_2O. Concentration in vacuo gave diesters **31a** (231 mg, 100%) as a white solid, which was a ∼2:1 mixture of *E*/*Z* isomers by NMR.

3-(2-Carboxy-2-(pyridin-2-yl)vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 32b from 27b via 29b and 31b. The ketene silyl acetal **28b** was prepared from ethyl 2-pyridylacetate as described in general procedure III to afford silyl ether **29b** (1.178 g). The early and late fractions containing minor impurities were recrystallized from Et_2O/pentane to give a second and third crop of crystals (overall yield of 1.804 g, 61%, a mixture of erythro/threo isomers) as fine ivory crystals: mp 161−176 °C. IR (KBr): ν_{max} 1732, 1719, 1248, 1211, 1177, 1082, 843 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.82 and 10.71 (s and bs, 0.2 H), 9.32, 9.30, 9.23 and 8.84 (major) (4 s, 1 H), 8.62 and 8.23 (major) (2 m, 1 H), 7.13−7.72 (m, 5 H), 6.88−6.97 (m, 1 H), 6.79, 6.75 (major) and 6.72 (3 d, 1 H, J = 10.3, 10.5, and 10.3 Hz, respectively), 5.19, 5.17 (major), 4.99 (major), and 4.98 (4 d, 1 H, J = 9.9, 10.2, 10.4 and 10.3 Hz, respectively), 4.12−4.56 (m, 4 H), 3.73−3.86 (m, 0.6 H), 1.36−1.53 (m, 4 H), 1.29 (t, 2 H, J = 7.1 Hz), 0.75−0.85 (m, 1 H), −0.05, −0.06, −0.31, and −0.33 (4 s, 9 H). MS: *m/z* 525, 524, 523 (M^+ + 1), 522 (M^+), 509, 507, 487, 435, 433, 360, 358 (100). Anal. $C_{24}H_{28}Cl_2N_2O_5Si$: C, H, N.

Silyl ether **29b** (577 mg, 1.10 mmol) was treated (vide supra) with Tf_2O (200 μL, 1.19 mmol) to afford diester **31b** (195 mg of >95% pure *E*) as fine white crystals. Recrystallization/trituration of the oily yellow mother liquor with Et_2O gave an additional 254 mg (449 mg total, 49%) of light yellow crystals containing a small amount of aldehyde from the retro-aldol reaction. For **31b**: mp 152−153 °C (dec). IR (KBr): ν_{max} 1717, 1248 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.05 (bs, 1 H), 8.44 (ddd, 1 H, J = 4.8, 1.8, 1.0 Hz), 8.26 (s, 1 H), 7.36 (td, 1 H, J = 7.8, 1.8 Hz), 7.22 (d, 1 H, J = 1.7 Hz), 7.10 (d, 1 H, J = 1.7 Hz), 7.0 (m, 2 H), 4.36 (q, 2 H, J = 7.1 Hz), 4.22 (q, 2 H, J = 7.1 Hz), 1.42 (s, 3.6 H, cyclohexane), 1.34 (2t, 6 H, J = 7.1 Hz). MS: *m/z* 473 (M^+ + 41), 463, 461 (M^+ + 29), 435, 433 (M^+ + 1, 100), 361, 359. Anal. $C_{21}H_{18}Cl_2N_2O_4 \cdot 0.3C_6H_{12}$: C, H, N.

Hydrolysis of diester **31b** (429 mg, 0.991 mmol) gave **32b** (as the *E* isomer) which upon drying in vacuo at 125 °C isomerized to a 6:1 *E*/*Z* mixture of isomers: mp 187−189 °C (dec). IR (KBr): ν_{max} 3426, 1684, 1611, 1240 cm^{-1}. ^1H NMR (DMSO-d_6); *E* isomer only: δ 13.2 (bs, 2 H), 12.23 (s, 1 H), 8.33 (dm, 1 H, J = 4.8 Hz), 8.16 (s, 1 H), 7.54 (td, 1 H, J = 7.8, 1.8 Hz), 7.35 (d, 1 H, J = 1.8 Hz), 7.13 (d, 1 H, J = 1.8 Hz), 7.1 (m, 1 H), 7.01 (dt, 1 H, J = 7.9, 1.0 Hz). MS: *m/z* 405 (M^+ + 29), 379, 377 (M^+ + 1), 335, 333 (100), 291, 289, 288, 287, 260, 258, 253. Anal. $C_{17}H_{10}Cl_2N_2O_4 \cdot 0.8H_2O$: C, H, N.

3-[2-Carboxy-2-(3-methoxyphenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 32c from 27c via 30c and 31c. Methyl (*m*-methoxyphenyl)acetate (**27c**) was prepared according to a literature procedure.[32] The spectra agreed with the published spectra.

The aldol condensation was carried out as described in general procedure III using 1-methoxy-1-(trimethylsiloxy)-2-(*m*-methoxyphenyl)ethylene (**28c**). The erythro/threo alcohols **30c** (2.42 g, 31%) were obtained as a white powder, including pure threo alcohol **30c** (0.85 g) as a white powder: mp 252 °C (dec). IR (KBr): ν_{max} 3401, 1736, 1690, 1611, 1559, 1435, 1319, 1242, 1165 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.96 (bs, 1 H), 7.13 (d, 1 H, J = 1.6 Hz), 7.03 (bs, 1 H), 6.89 (t, 1 H, J = 8.0 Hz), 6.80 (bs, 1 H), 6.67 (dd + m, 2 H, J = 11.3, 10.1 Hz), 6.54 (ddd, 1 H, J = 8.2, 2.5, 0.9 Hz), 5.26 (bs, 1 H), 4.49 (q, 2 H, J = 7.1 Hz), 4.39 (m, 1 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 1.48 (t, 3 H, J = 7.1 Hz)—plus minor impurities. ^{13}C NMR ($CDCl_3$): δ 172.9, 159.1, 136.3, 131.3, 128.9, 123.3, 121.2, 113.9, 110.4, 67.7, 62.4, 59.1, 55.1, 52.3, 14.3. MS: *m/z* 494 (M^+ + 29), 466 (M^+ + 1), 448, 416, 286 (100), 181, 149, 121. Anal. Calcd for $C_{22}H_{21}Cl_2NO_6$.

Dehydration of the *m*-methoxy aldol products **30c** gave **31c** (1.5 g, 63%, ∼3:2 ratio of *E*/*Z* isomers) as a ivory powder: mp 147−150 °C. IR (KBr): ν_{max} 3302, 1717, 1678, 1609, 1559, 1435, 1321, 1289, 1242, 1179 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.34 (bs, 1 H *Z* isomer), 9.15 (bs, 1 H *E* isomer), 8.18 (s, 1 H *E* isomer), 7.45 (s, 1 H *Z* isomer), 7.33 (t, 1 H *Z* isomer, J = 7.9 Hz), 7.16 (d, 1 H *E* isomer, J = 1.7 Hz), 7.1 (m, 2 H *E* isomer + 2 H *Z* isomer), 7.01 (m, 1 H *E* isomer), 6.92 (m, 1 H *Z* isomer), 6.7−6.6 (m, 2 H *E* isomer + 2 H *Z* isomer), 4.34 (t, 2 H *E* isomer, J = 7.1 Hz), 4.27 (t, 2 H *Z* isomer, J = 7.1 Hz), 3.86 (s, 3 H *E* isomer), 3.85 (s, 3 H *Z* isomer), 3.59 (s, 3 H *Z* isomer), 3.54 (s, 3 H *E* isomer), 1.35 (t, 3 H *E* isomer, J = 7.1 Hz), 1.32 (t, 3 H *Z* isomer, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 167.7, 167.3, 161.4, 160.8, 159.4, 158.5, 139.7, 137.1, 136.9, 136.7, 136.5, 136.4, 134.2, 131.6, 131.2, 131.0, 129.2, 128.6, 128.5, 128.4, 124.9, 124.6, 123.6, 122.4, 122.3, 122.2, 120.7, 118.1, 117.3, 115.3, 114.0, 113.4, 113.2, 110.5, 110.5, 61.5, 55.3, 54.9, 52.4, 51.8, 14.2, 14.1. MS: *m/z* 476 (M^+ + 29), 447 (M^+), 416 (100). Anal. $C_{22}H_{19}Cl_2NO_5$: C, H, N.

Hydrolysis (vide supra) of the diesters **31c** gave, after flash chromatography (5−7% AcOH/CH_2Cl_2) and recrystallization from acetone/H_2O, **32c** (640 mg, 49%) as a ivory powder: mp 269 °C (dec). IR (KBr): ν_{max} 3414, 3405, 3352, 1690, 1613, 1559, 1289, 1248, 1215 cm^{-1}. ^1H NMR (DMSO-d_6): δ 13.03 (bs, 2 H), 12.15 (s, 1 H), 8.05 (s, 1 H), 7.33 (d, 1 H, J = 1.7 Hz), 7.16 (d, 1 H, J = 1.7 Hz), 7.00 (t, 1 H, J = 8.0 Hz), 6.64 (ddd, 1 H, J = 8.3, 2.6, 1.0 Hz), 6.5−6.6 (m, 2 H), 3.52 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ 167.6, 161.6, 157.9, 137.1, 136.8, 136.8, 133.8, 128.7, 128.1, 127.1, 126.7, 122.5, 121.9, 120.7, 115.6, 115.4,

112.2, 111.1, 54.5. MS: *m/z* 416, 405 (M^+), 388 (100). Anal. $C_{19}H_{13}Cl_2NO_5$: C, H, N.

3-[2-Carboxy-2-(3-phenoxyphenyl)vinyl]-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 32d from 27d via 29d/30d and 31d. Methyl (*m*-phenoxyphenyl)acetate **27d** was prepared according to the literature procedure.[32] ^{1}H NMR ($CDCl_3$): δ 7.2−7.4 (m, 4 H), 7.14 (m, 1 H), 7.0 (m, 4 H), 3.73 (s, 3 H), 3.64 (s, 2 H).

Mukaiyama coupling of aldehyde **6** (2.0 g, 7.0 mmol) with the ketene silyl acetal **28d**, prepared from **27d** (5.08 g, 21.0 mmol) was carried out as described in general procedure III to afford TMS ethers **29d** (0.92 g, 22%) and alcohols **30d** (1.27 g, 34%).

Alcohols **30d** (1.27 g, 2.40 mmol) were treated with *p*-TsOH·H_2O (40 mg, 0.21 mmol) to afford crude diester **31d**. ^{1}H NMR (DMSO-d_6): δ 12.35 (d, 1 H), 8.1 (s, 1 H), 7.0−7.5 (m, 5 H), 6.9 (d, 2 H), 6.8 (2 H), 6.7 (2 H), 4.1−4.4 (m, 2 H), 2.5 (s, 3 H), 1.1−1.3 (3 H).

Hydrolysis of diester **31d** (1.19 g, 2.32 mmol) provided **32d** as a yellow crystalline solid. IR (KBr): ν_{max} 3418, 3283, 1686, 1613, 1489, 1240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.20−13.60 (bs, 2H), 12.20 (s, 1 H), 8.10 (s, 1 H), 7.35 (m, 4 H), 7.18 (s, 1 H), 7.09 (m, 1 H), 6.96 (d, 2 H, J = 8.8 Hz), 6.82 (d, 2 H, J = 8.8 Hz), 6.72 (d, 2 H, J = 8.8 Hz). MS: *m/z* 468 ($M^+ + 1$), 450 ($M^+ + 1 - H_2O$), 424. Anal. $C_{24}H_{15}Cl_2NO_5 \cdot 0.9\ C_4H_{10}O$: C, H, N.

3-(2-Carboxy-3-phenylpropenyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 32e. The ketene silyl acetal of methyl hydrocinnamate (**28e**) was prepared and coupled with **6** as previously described to give 2.0 g (36%) of diester ***Z*-31e** as a white solid: mp 150−150.5 °C. IR (KBr): ν_{max} 3304, 3086, 3063, 3028, 2986, 2951, 2910, 2847, 1803, 1709, 1651, 1610, 1557 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.36 (bs, 1 H), 7.32−7.41 (m, 4 H), 7.22−7.27 (m, 1 H), 7.14 (bt, 1 H, J = 1.3 Hz), 7.04 (d, 1 H, J = 1.7 Hz), 7.00 (d, 1 H, J = 1.7 Hz), 4.27 (q, 2 H, J = 7.2 Hz), 3.89 (bs, 2 H), 3.57 (s, 3 H), 1.31 (t, 3 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 167.5, 161.1, 138.8, 136.7, 134,9, 132.3, 130.5, 129.2, 128.4, 128.3, 126.4, 124.5, 122.3, 122.1, 118.3, 110.6, 77.3, 77.0, 76.7, 61.3, 51.5, 40.5, 14.2. MS: *m/z* 460 ($M^+ + 29$), 432 ($M^+ + 1$), 400 (100). Anal. $C_{22}H_{19}Cl_2NO_4$: C, H, N.

Hydrolysis of diester **31e** (575 mg, 1.33 mmol) with 6 N NaOH (2 mL) and heating at 80 °C for 1 h, followed by acidic workup and recrystallization (acetone/H_2O), afforded diacid ***Z*-32e** (484 mg, 93%) as a white solid: mp 244−244.5 °C (dec). IR (KBr): ν_{max} 3387, 3346, 3084, 3065, 3028, 2714, 2596, 1689, 1614, 1558 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.66 (bs, 1.5 H), 12.14 (s, 1 H), 7.39 (d, 1 H, J = 2.1 Hz), 7.24−7.37 (m, 4 H), 7.16−7.23 (m, 1 H), 7.20 (bs, 1 H), 7.14 (d, 1 H, J = 1.8 Hz), 3.76 (s, 2 H). ^{13}C NMR (DMSO-d_6): δ 167.6, 162.3, 139.5, 136.9, 135.1, 130.8, 128.8, 128.3, 128.1, 127.6, 126.3, 125.9, 122.3, 120.6, 117.5, 111.1, 40.2. MS: *m/z* 400 ($M^+ + 29$), 390 ($M^+ + 1$), 389 (M^+), 390 ($M^+ - H_2O$, 100). Anal. $C_{19}H_{13}Cl_2NO_4 \cdot 0.2H_2O$: C, H, N.

4,6-Dichloro-3-(2-(methoxycarbonyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-1*H* -indole-2-carboxylic Acid Ethyl Ester, 31f. Ketene acetal **28f** was generated from methyl 4-phenylbutyrate **27f** (4.2 g, 23.6 mmol) and was reacted with **6** (3.7 g, 12.85 mmol) as described in the general procedure III to afford **31f** directly (2.0 g, 35%; ca. 1:1 mixture of diastereomers) as a white solid: mp 165−166.5 °C. IR (KBr): ν_{max} 3331, 3099, 3061, 3018, 2992, 2982, 2949, 2865, 2843, 1718, 1697, 1610, 1556, 1523, 1489, 1437, 1369, 1350, 1319, 1280, 1236, 1172, 1114 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 and 9.11 (two brs, 1 H), 7.25 and 7.22 (two d, 1H, J = 2 Hz), 7.17 and 7.00 (two d, 1H, J = 2 Hz), 6.89−7.14 (series of m, 3H), 6.69 (m, 1H), 5.97 and 5.82 (two d, 1H, J = 11 Hz), 4.45 and 4.10 (two AB-m, 2H), 3.59 (m, 1H), 3.49 and 3.47 (two s, 3H), 2.92−3.22 (m, 2H), 2.06−2.36 (m, 2H), 1.42 and 1.02 (two t, 3H, J = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$; multiplicities derived from APT spectrum): δ 175.6 s, 175.3 s, 161.9 s, 160.3 s, 139.5 s, 139.1 s, 137.9 s, 136.3 s, 135.6 s, 135.5 s, 130.9 s, 130.6 s, 128.8 s, 128.4 d, 128.1 s, 128.0 d, 127.7 d, 127.6 d, 127.4 s, 126.2 s, 126.0 d, 125.9 d, 125.6 d, 125.3 d, 124.9 s, 123.9 s, 123.5 s, 123.2 d, 122.8 d, 122.3 s, 110.6 d, 110.4 d, 61.6 t, 61.1 t, 51.5 q, 51.4 q, 47.8 d, 47.1 d, 38.3 d, 38.0 d, 29.2 t, 29.0 t, 27.4 t, 27.2 t, 14.3 q, 13.8 q. CIMS (CH_4): *m/e* (rel intens) 474 ($M + C_2H_5^+$, 8), 446 ($M + H^+$, 24), 385 ($M^+ - HCO_2Me$), 189 (100). Anal. $C_{23}H_{21}Cl_2NO_4$: C, H, N.

4,6-Dichloro-3-(2-cyclohexyl-2-(methoxycarbonyl)vinyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 31g. Mukaiyama coupling of aldehyde **6** (1.20 g, 4.19 mmol) with the ketene silyl acetal **28g**, prepared from methyl cyclohexylacetate **27g** (1.97 g, 12.6 mmol), as described in the general procedure III gave alcohols **29g** (0.62 g, 33%). Dehydration of alcohols **29g** (629 mg, 1.40 mmol) in toluene (10 mL) with *p*-TsOH·H_2O (30 mg, 0.16 mmol) for 12 h gave, after recrystalization from hot CH_2Cl_2, diester ***Z*-31g** (382 mg, 64%) as a yellow powder. ^{1}H NMR ($CDCl_3$): δ 9.23 (s, 1 H), 7.29 (s, 1 H), 7.16 (m, 1 H), 7.08 (d, 1 H), 4.35 (q, 2 H), 3.5 (s, 3 H), 1.6−2.05 (m, 5 H), 1.2−1.5 (m, 9 H).

3-(2-Carboxy-2-cyclohexylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 32g. Hydrolysis (vide supra) of diester ***Z*-31g** (382 mg, 0.90 mmol) in THF (5 mL) using 1 M NaOH (5.5 mL) gave *Z*-ester acid (250 mg, 71%) in which the methyl ester of the side chain had remained unhydrolyzed. IR (KBr): ν_{max} 3300, 2928, 2855, 1694, 1556, 1535, 1248 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.5 (br, 1 H), 12.02 (s, 1 H), 7.39 (d, 1 H, J = 1.8 Hz), 7.15 (d, 1 H, J = 1.8 Hz), 7.06 (s, 1 H), 1.60−1.94 and 1.12−1.42 (m, 11 H). ^{1}H NMR (DMSO-d_6 + D_2O): δ 3.34 (s, $-CO_2Me$). MS: *m/z* 396 ($M^+ + 1$), 364 ($M^+ - MeOH$), 336. Anal. Calcd for $C_{19}H_{19}Cl_2NO_4$: C, 57.89; H, 4.86; N, 3.55. Found; C, 56.50; H, 4.64; N, 3.35. Further hydrolysis of the *Z*-ester acid as above for an additional 12 h gave, after acidification and recrystallization from EtOAc/cyclohexane, diacid ***Z*-32g** (192 mg, 55.8%) as white crystals. IR (KBr): ν_{max} 3279, 2930, 2857, 1696, 1559, 1451, 1248, 1203 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.3−12.3 (br, 2 H), 12.05 (s, 1 H), 7.37 (d, 1 H, J = 1.8 Hz), 7.12 (d, 1 H, J = 1.8 Hz), 6.93 (s, 1 H), 1.63−1.91 (m, 5 H), 1.10−1.42 (m, 6 H). MS (CI, NH_3): *m/z* 401, 399 ($M^+ + NH_4$, 100), 381 ($M^+ + NH_4^+ - H_2O$), 355, 96. Anal. $C_{18}H_{17}Cl_2NO_4$: C, H, N.

4,6-Dichloro-3-(hydroxymethyl)-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 33. $NaBH_4$ (1.10 g, 29 mmol) was added to a stirred solution of *N*-tosyl aldehyde **7** (12.3 g, 28 mmol) in THF (125 mL), and the reaction mixture was stirred for 2 h at 35 °C. The THF was evaporated, and H_2O (50 mL) was added to the residue. The H_2O layer was extracted with EtOAc (2 × 80 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give alcohol **33** (10.7 g, 87%) as a white solid. ^{1}H NMR (DMSO-d_6): δ 7.99 (s, 1 H), 7.85 (m, 2 H), 7.28 (m, 3 H), 4.95 (s, 2 H), 4.51 (q, 2 H, J = 7.1 Hz), 2.39 (s, 3 H), 1.42 (t, 3 H, J = 7.1 Hz).

4,6-Dichloro-3-(chloromethyl)-1-(toluene-4-sulfonyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 34. A mixture of alcohol **33** (5.0 g, 11 mmol), $SOCl_2$ (1.5 mL, 20 mmol), and toluene (50 mL) was heated at reflux for 1 h. The reaction mixture was concentrated in vacuo to give chloride **34** (5.2 g, 100%) as a dark brown solid, which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 7.82−7.98 (m, 3 H), 7.23−7.37 (m, 3 H), 4.95 (s, 2 H), 4.52 (q, 2 H, J = 7.2 Hz), 2.40 (s, 3 H), 1.45 (t, 3 H, J = 7.1 Hz).

4,6-Dichloro-3-(2-(ethoxycarbonyl)-2-phenylethyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester, 35. To the crude chloride **34** (5.2 g, 11 mmol) dissolved in THF (15 mL) was added NaI (1.7 g, 11 mmol), and the reaction mixture was stirred at rt under N_2 for 4 h. In a separate reaction flask, the anion of ethyl phenylacetate (6.0 g, 36 mmol) was generated in THF (75 mL) by the addition of NaH (1.6 g, 36 mmol, 55% dispersion in oil). After stirring for 3 h at 40 °C, the resulting yellow suspension was cooled to −40 °C and the crude chloride **34**/NaI/THF solution was added. The reaction mixture was allowed to warm to rt and stirred for 18 h, after which it was diluted with H_2O (150 mL), extracted with Et_2O (3 × 80 mL), dried (Na_2SO_4), and concentrated in vacuo to give a crude brown solid. Recrystallization from 9:1 hexane/EtOAc gave dihydro diester **35** (1.5 g, 30%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.90 (br s, 1 H), 7.25 (d, 1 H, J = 2 Hz), 7.14−7.20 (m, 5 H), 7.15 (d, 1 H, J = 2 Hz), 3.98−4.40 (overlapping q, 4

H), 3.98−4.15 (m, 2 H), 3.75−3.92 (m, 1 H), 1.41 (t, 3 H, J = 7 Hz), 1.16 (t, 3H, J = 7 Hz).

3-(2-Carboxy-2-phenylethyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 36. The dihydro diester **35** (820 mg, 1.9 mmol) was heated at reflux in a mixture of KOH (700 mg, 10.6 mmol) and EtOH (50 mL). After 16 h, the EtOH was evaporated and the residue acidified to pH 1 with aqueous HCl. The precipitate formed was washed with H_2O and dried to provide dihydro diacid **36** (600 mg, 86%) as a white solid. Precipitation of the crude product from EtOH with 2-butanone gave the pure dihydro diacid **36** (390 mg, 56%) as a white solid.

3-(2-Carboxy-2-phenylethyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid, 36 from 29a via 37. To a stirred solution of aldol **29a** (395 mg of the less polar diastereomer, 0.905 mmol) in dry CH_2Cl_2 (4 mL) under N_2 was added Et_3SiH (200 μL, 1.25 mmol) followed by TFA (0.90 mL). After stirring for 16 h at rt, the reaction mixture was diluted with EtOAc/Et_2O, washed with H_2O (2×), and concentrated in vacuo to give 700 mg of a light yellow solid. Recrystallization from cyclohexane/trace EtOAc gave diester **37** (320 mg, 84%) as a white solid: mp 160−164 °C (dec). IR (KBr): ν_{max} 3325, 1734, 1715, 1701, 1676, 1321, 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.88 (bs, 1 H), 7.24 (d, 1 H, J = 1.7 Hz), 7.15−7.25 (m, 5 H), 7.13 (d, 1 H, J = 1.7 Hz), 4.35 (dq, 1 H, J = 11, 7 Hz), 4.23 (dq, 1 H, J = 11, 7 Hz), 4.07−4.15 (m, 2 H), 3.79−3.88 (m, 1 H), 3.60 (s, 3 H), 1.40 (t, 3 H, J = 7.1 Hz). MS: *m/z* 422, 421, 420 (M^+ + 1), 419, 390, 388, 362, 360 (100), 272, 270. Anal. $C_{21}H_{19}Cl_2NO_4$: C, H, N.

Hydrolysis of diester **37** (320 mg, 0.76 mmol) in 5:1 THF/H_2O (24 mL) using LiOH·H_2O (95 mg, 2.3 mol) at reflux for 5 h gave 350 mg of yellow solid. Recrystallization from cyclohexane/EtOAc gave **36** (280 mg, 74.0%) as fine ivory needles: mp 246−248 °C (dec). IR (KBr): ν_{max} 1699 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.18 (br s, 1 H), 12.37 (br s, 1 H), 11.87 (s, 1 H), 7.35 (d, 1 H, J = 1.8 Hz), 7.1−7.22 (m, 5 H), 7.15 (d, 1 H, J = 1.8 Hz), 3.98 (dd, 1 H, J = 8.3, 7.1 Hz), 3.90 (dd, 1 H, J = 13.4, 7.0 Hz), 3.78 (dd, 1 H, J = 13.4, 8.7 Hz). MS: *m/z* 379, 378 (M^+ + 1), 377, 334, 332 (100), 244, 242. Anal. $C_{18}H_{13}Cl_2NO_4$: C, H, N.

Receptor Binding. Affinity for brain strychnine glycine binding on the NMDA receptor complex were performed using rat cortical and hippocampal membranes.[33,34] Approximately 50−60 young male Sprague−Dawley rats (C−D strain) were sacrificed by decapitation and their cerebral cortices and hippocampi removed. The two brain regions were combined and homogenized in 15 volumes of ice-cold 0.32 M sucrose using Teflon glass homogenized (10 passes at 400 rpm). The homogenates were centrifuged at 1000*g* for 10 min, and the supernatants were transferred and recentrifuged at 44,000 x gravity for 20 min. The upper white part of the pellets were suspended with a pipet in ice-cold water and homogenized with a polyron (setting 6 for 10 s) and centrifuged at 44000*g* for 15 min. Pellets were then suspended in 6 volumes of water and placed in a dry ice/methanol bath until frozen, followed by thawing at 37 °C in a shaking water bath. The freeze/thaw process was repeated, and the final volumes of the suspension were adjusted to 15 volumes with water and centrifuged at 44000*g* for 15 min. The resulting pellets were then suspended in 15 volumes of 10 mM HEPES−KOH (*N*-2-(hydoxyethyl)-piperazine-*N*′-2-ethanesulfonic acid−potassium hydroxide) at pH 7.4 containing 0.04% Triton X-100 (v/v), incubated at 37 °C for 15 min and centrifuged at 44000*g* for 15 min. The pellets were resuspended in 15 volumes of 10 mM HEPES−KOH at pH 7.4 with a polytron (setting of 6 for 10 s) and centrifuged at 44000*g* for 15 min. This resuspension/centrifugation process was repeated an additional 2 times. The membranes were then resuspended in 3 volumes of 10 mM HEPES and stored at −80 °C.

When the assay was to be performed, the membranes were thawed at ambient temperatue and diluted with 9 volumes of 10 mM HEPES−KOH, pH 7.4, and incubated at 25 °C for 15 min. This was followed by centrifugation at 44000*g* for 15 min and then resuspension with 10 mM HEPES−KOH at pH 7.4 using a polytron. The incubation/resuspension process was repeated an additional 2 times, and the final pellet was resuspended in 6 volumes of 50 mM HEPES−KOH at pH 7.4. Incubation vials, in triplicate, received 50 μL of 200 nM [^{3}H]-glycine, 50 μL of 100 nM strychnine, 50 μL of various concentrations of test compounds diluted with 50 mM HEPES−KOH at ph 7.4, and 200 μL of membrane suspension (400 μg of protein/aliquot) in a final volume of 0.5 mL. Incubations were carried out at 4 °C for 30 min and were terminated by centrifugation at 46000*g* for 10 min. The supernatants were decanted, and the pellets were rinsed rapidly with 2 mL of ice-cold 50 mM HEPES−KOH at pH 7.4, then dissolved in 4 mL of Ready Protein (Beckman Instruments), and counted by liquid scintillation spectrometry.

Specific binding of [^{3}H]glycine is measured as the total radioactivity bound minus that bound to the receptors in the presence of 0.1 mM D-serine. Total membrane-bound radioactivity is less that of the 2% added to the assay vials. Since these conditions limit the total binding to less than 10% of the radioactivity, the concentration of free ligand does not change appreciably during the assay. The IC_{50} values reported represent the molar concentration of a compound required to reduce glycine binding by 50%, and were mean values from two or more experiments; standard errors in all cases were within 10−30% of the mean.

Quinolinic Acid Seizures. One group of 10 mice (CD-1 mice) were administered 0.01−100 μg of test compound intracerebroventricularly (icv) in a volume of 5 μL of saline.[35] A second control group containg an equal number of mice were administered an equal volume of saline as a control. Approximately 5 min later, both groups were administered 7.7 μg of quinolinic acid icv in a volume of 5 μL of saline. This dose of quinolinic acid was found to cause clonic−tonic seizures in 90−100% of otherwise untreated mice. Immediately following quinolinic acid administration, animals were observed for the next 15 min for the occurrence of clonic−tonic seizures. Those mice not convulsing during the observation period were considered protected. The ED_{50} is defined as that dose that protects 50% of the mice.

NMDA-Elicited Cyclic cGMP. The most potent compounds, **11h** and **19**, were confirmed as antagonists by their ability to inhibit NMDA-stimulated accumulation of cyclic GMP. Similar assays were run with known NMDA antagonists **38** (CoCensys), **39** (Glaxo), and **40** (Merck) in order to evaluate the affinity of the compounds for the glutamic acid binding site of the NMDA receptor complex. NMDA-elicited cyclic GMP (cGMP) was measured in 8-day old CD rat cerebellar slices. Cystolic free Ca^{2+} concentrations were measured in fur-2 AM-loaded cultured rat cerebellar granule cells (8 days in vitro) using microspectrofluorimetry.[35] Na^+ and Ca^{2+} currents were measured by the whole-cell configuration of the patch-clamp technique. Rat brain neurons (CD rat, 4−18 days in vitro) were continually perfused at 0.5 mL/min at 22 °C in a HEPES buffered extracellular saline solution consisting of the following (mM): 142 NaCl; 1 $CaCl_2$; 8 KCl; 10 glucose; and 10 HEPES, pH 7.4. Patch pipets were fabricated from Fisher brand microhematocrit capillary tubes and filled with an intracellular solution consisting of the following (mM): 153 $CsCl_2$; 10 HEPES; and 5 EGTA, pH 7.38. Test compounds were prepared as 10 mM stock solutions in DMSO. Immediately prior to use, appropriate concentrations were prepared by dilution with external solution (DMSO final concentration ranged from 0.001 to 1.0%). NMDA (100 μM)/glycine (2 μM) and/or test compounds were applied via a U-tube (rapid solution exchanger) positioned within 200 μm of the neuron of interest. Via this method a complete solution change in the vicinity of a cultured neuron was achieved well within 500 ms.[36] The relative potencies of test compounds were assessed by comparison of the response to NMDA (100 μM)/ glycine (2 μM) obtained in

the presence of the antagonist relative to that elicited by NMDA/glycine alone. Recordings from 3 to 8 cells were collected for each compound examined. All cells successfully patched responded to NMDA/glycine.

Harmaline-Elevated Cyclic GMP. Inhibition of harmaline-elevated cyclic GMP accumulation was measured in the cerebellum of CD-1 mice.[37] Cyclic GMP content was normalized to the amount of membrane protein. Rat brain (CD rat) dihydroxyphenylalanine accumulation and extracellur dopamine levels were assayed according to procedures reported.[38−40]

Maximal Electroshock. Maximal electroshock-induced seizure testing was performed using CDF rats.[41] Assessment of anxiolytic potential was performed using the separation-induced vocalization test in CD rat pups.[42,43] Assessment of potential ataxia was measured by disruption of rotorod performance in CD-1 mice[41] or by the ability of a compound to decrease the amount of time that an 8-day old CD rat pup was able to retain its grasp on the lip of an ice bucket.[43] Effects of compounds on sensory gating were assessed by their measured effect on prepulse inhibition of the startle reflex in Wistar rats.[41]

DBA Audiogenic Seizure.[44] Typically one group of six to eight male DBA/2J audiogenic susceptible mice was administered 0.01−10.0 μg of the test compound, as a solution in methylcellulose, into the lateral ventricle of the brain or from 0.1 mg to 300 mg intraperitoneally. A second group of mice was administered an equal volume of a saline control by the same route. A period of 5 min to 4 h later, the mice were placed individually into a glass jar and exposed to a sound stimulus of 110 dB (12 kHz) for 30 s. Each mouse was observed during the sound exposure for signs of seizure activity. Mice not displaying tonic hind limb extension were considered protected. Animals treated with probenecid were coadministered probenecid (100 mg/kg, ip) and test compound 1 h prior to the seizure stimulus.

dMCAo and pMCAo Focal Cerebral Ischemia Models.[45,46] Compound **19** was administered at three doses vs saline vehicle in the dMCAo (distal middle cerebral artery occlusion) model. Drug administration was begun with a bolus dose given 15 min prior to the onset of ischemia and maintained by continuous infusion. The highest dose of **19** (70 mg/kg bolus + 70 mg/kg/h infusion for 6 h) showed significant neuroprotection reducing infarct volume by 32%. While the dose of 35 mg/kg + 35 mg/kg/h for 6 h demonstrated a trend toward neuroprotection (12% reduction of infarct volume), it did not reach statistical significance. This experiment validates the concept that a molecule of this structural type can provide significant infarct volume reduction in a severe ischemia model. These results were used to establish the upper dose level for postocclusion testing in the dMCAo and the ischemia-reperfusion pMCAo (proximal middle cerebral artery occlusion) models and serve as a starting point for dose optimization.

A second study employed poststroke administration of **19** in the dMCAo model. Drug treatment was initiated 30 min after the onset of ischemia. A dosing regimen of 35 mg/kg bolus + 25 mg/kg/h infusion for 4 h was used and resulted in a 28% reduction in infarct volume, which is similar to that achieved with preischemia dosing.

Antagonists **19** and **11h** and all competitor compounds were administered iv, the desired route of administration for acute stroke treatment. Anticonvulsant experiments in mice and rats indicated that the half-life of effect for **19** and **11h** was approximately 30 min to 1 h. Therefore, in the stroke experiments, sustained administration would be required to provide NMDA antagonism during the period of excitotoxic cell death. Bolus doses of **19** and **11h** were chosen to be within the range necessary for anticonvulsant activity measured with the rat maximal electroshock test. Preliminary pharmacokinetic information was obtained to define the appropriate values for infusion doses. This allowed maintenance of steady-state plasma drug concentrations, providing a sustained pharmacological effect.

Following this initial demonstration of efficacy in the pMCAo model, the results were extended to include postocclusion dosing. The dosing regimen was as in the previous experiment (bolus + 6 h infusion) but was initiated 30 min after the onset of ischemia. Compound **19** produced a dose-dependent reduction in infarct volume. This was significant at doses of 4.5 mg/kg bolus + 4.5 mg/kg/h × 6 h infusion (total dose of 31.5 mg/kg) and above but not at the lowest dose (2.25 mg/kg bolus + 2.25 mg/kg/h × 6 h infusion). Therefore, the minimal effective dose (MED) is 31.5 mg/kg given over 6 h. In two separate experiments, drug concentrations were measured in plasma samples from rats receiving the bolus + infusion regimen corresponding to the MED. Plasma concentrations of **19** ranged from 21 to 25 μg/mL.

Reduced infarct volume in rats using MCAo was determined using male Sprague−Dawley rats.[45] The rat is anesthetized with halothane in a mixture of O_2 and NO (1:2 ratio) and a midline incision is made in the ventral neck region. An indwelling venous catheter is placed in the jugular vein. Under a dissecting microscope, the left common carotid artery is identified at its bifurcation into the external carotid artery and internal carotid artery. Two ties are placed on the external carotid artery. The internal carotid artery is exposed distally to the point of its bifurcation into the intracranial internal carotid artery and the pterygopalatine artery. A small cut is made in the distal segment of the external carotid artery and a 3-0 nylon monofilament is introduced into the lumen of the external carotid artery. The two previously placed ties are tightened around the monofilament. The external carotid artery is cut and reflected caudally so that the monofilament can be advanced into the internal carotid artery, past the distal internal carotid artery/pterygopalatine artery bifurcation and continuing into the intranial segment of the internal carotid artery to a distance of 20 nm, at which point the origin of the middle cerebral artery is occluded. The ties are then tightened, and the wound is closed. Compound or vehicle alone is administered intravenously at a predetermined time postischemia and dosing can be single, multiple, or continuous infusion. Animals are given food and water and allowed to survive for 24 h. Prior to sacrifice, the rat is weighed and given a battery of four neurological tests to measure muscle strength, grooming skills, postural reflexes, and sensorimotor integration.[46] The animal is then decapitated, the brain removed, sliced into six sections, and incubated in 2% 2,3,5-triphenyltetrazolium chloride for 30 min.[47] The area of infarction is clearly visible. The infarct area is determined by computer-assisted image analysis for each of the six sections and integrated over the anterior−posterior extent of the brain to yield the infarct volume.

Animals. Adult male mice (Charles River CD-1), alult male rats (Charles River CD, Wistar, or CDF), or 18 day old, male audiogenic seizure mice (DBA/2J Jackson Laboratories) were used for the in vivo studies. Neonatal (Charles River CD) rats were used for cell culture and brain slice experiments. Animals were housed in animal rooms on a 14 h light/dark cycle and allowed free access to food and water. Neonatal rats were housed with the mother in a breeding box with sawdust bedding. All experiments were performed during the light phase of the light/dark cycle. Drugs were dissolved in distilled water, saline, or 50 mM Tris base and injected at a volume of 1 mL/kg (rats) or 10 mL/kg (mice).

Data Analysis. Concentration−response data were fit to a logistic function using nonlinear regression analysis. Antagonist-induced responses (e.g., NMDA-stimulated cGMP formation) used a function of the following form: response $= B + MX^n/(K^n + X^n)$, where B = observed basal response, M = calculated maximal response, X = concentration of agonist, n = slope factor, and K = calculated EC_{50} of the agonist. Antagonist-induced inhibition of responses was fit using a similar model of the following form: inhibition $= 100X^n/(K^n + X^n)$, where X = concentration of antagonist, n = slope factor, and $K = IC_{50}$ of the antagonist. Dose−response data were fit using linear regression of log-transformed values.

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

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