4-Phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione Inhibitors of the Checkpoint Kinase Wee1. Structure−Activity Relationships for Chromophore Modification and Phenyl Ring Substitution

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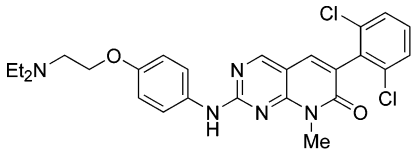
High-throughput screening has identified a novel class of inhibitors of the checkpoint kinase Wee1, which have potential for use in cancer chemotherapy. These inhibitors are based on a 4-phenylpyrrolo[3,4-*c*]-carbazole-1,3(2*H*,6*H*)-dione template and have been shown by X-ray crystallography to bind at the ATP site of the enzyme. An extensive study of the effects of substitution around this template has been carried out, which has identified substituents which lead to improvements in potency and selectivity for Wee1. While retention of the maleimide ring and pendant 4-phenyl group is necessary for potency, replacement of the carbazole nitrogen by oxygen is well tolerated and results in improved Wee1 selectivity against the related checkpoint kinase Chk1. Wee1 potency and selectivity are also enhanced by the incorporation of lipophilic functionality at the 2′-position of the 4-phenyl ring, and Wee1 selectivity against Chk1 is favored by C3−C5 alkyl substitution of the carbazole nitrogen. These studies provide a basis for the design of active analogues of the pyrrolocarbazole lead with improved physical properties.

Introduction

The protein tyrosine kinase enzyme Wee1 is involved in regulation of the DNA damage-sensitive G2/M checkpoint in the eukaryotic cell cycle, through its inhibitory phosphorylation of cdc2 on tyrosine 15.[1−3] Many cancer cells lack a functional p53 signaling pathway, which means that the other significant DNA damage-sensitive checkpoint, G1/S, is not controlled. Inhibitors of Wee1 should abrogate the G2/M checkpoint and should preferentially enhance the cytotoxic effects of DNA damaging agents on p53-negative cells by allowing them to bypass both of the checkpoints where damaged cells normally arrest to allow time for DNA repair. Coadministration of a Wee1 inhibitor with a conventional DNA-damaging cytotoxic agent in the clinic could therefore lead to improvements in responses to cancer therapy.[4−6]

We recently reported on the development of 6-phenylpyrido-[2,3-*d*]pyrimidin-7(8*H*)-ones (e.g., **1**, **2**) as inhibitors of Wee1,[7] and others have subsequently also noted Wee1 activity for this template.[8,9] Several of these were found to be potent Wee1 inhibitors (IC_{50} < 100 nM), but this activity could not be divorced from an even more potent inhibition of the kinase c-Src. Nevertheless, one of the more effective compounds (**1**) from this series was found to sensitize p53 mutant cells to the DNA damage induced by radiation.[10] In a high-throughput screening (HTS) program, we subsequently found that the 4-phenylpyrrolocarbazole **3** was an equally potent inhibitor of Wee1 (IC_{50} = 97 nM) while proving inactive against c-Src (IC_{50} > 50 μM).



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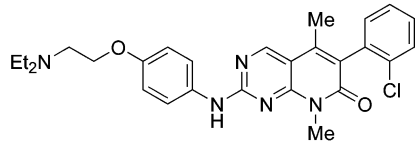

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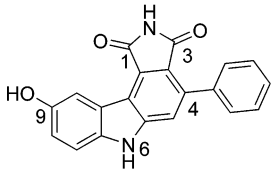

3

Wee1 IC_{50} = 97 nM
Chk1 IC_{50} = 47 nM
PKC IC_{50} = 3.4 μM
c-Src IC_{50} >50 μM
PDGFR IC_{50} >50 μM
FGFR IC_{50} >50 μM
CDK4 IC_{50} = 3.75 μM
Other CDKs >5 μM

Although the HTS lead **3** was originally prepared in a program directed toward the development of inhibitors of the protein kinase C family of serine−threonine kinases,[11] it had only low activity against these. The lead **3** was also poorly active against a series of receptor tyrosine kinases and cyclin-dependent kinases. However, **3** did display potent inhibition of Chk1

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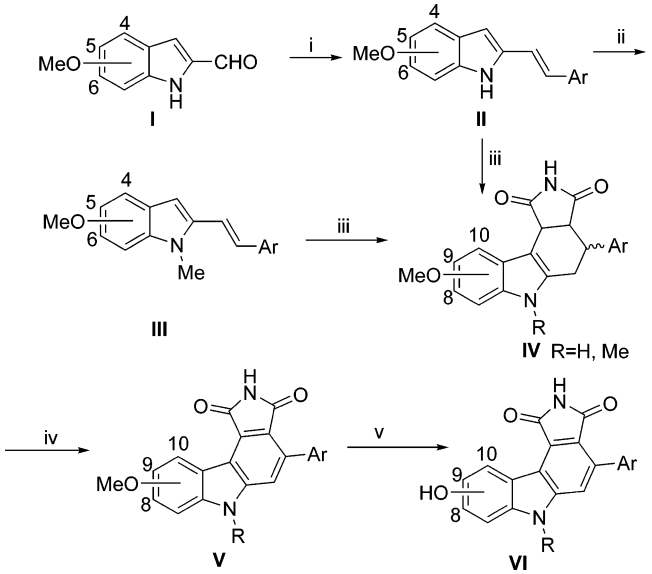
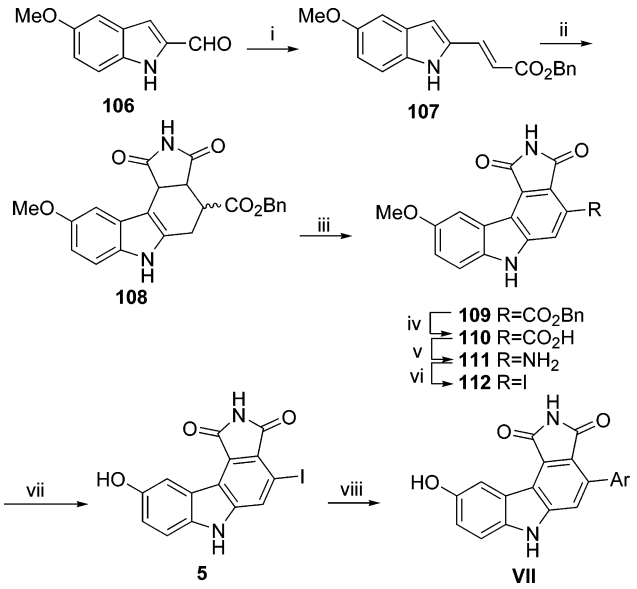
Scheme 1[a]



[a] Reagents and conditions: (i) $[Ph_3PCH_2Ar]X$, LDA, THF, reflux, 5 h; (ii) NaH, MeI, 20 °C, 15 min; (iii) maleimide, 175 °C, melt, 2−5 h; or maleimide, toluene, catalyst $SnCl_2$, reflux, 3 h to 6 days; (iv) MnO_2, dioxane, reflux, 5−24 h; or DDQ, toluene−dioxane, reflux, 6−48 h; (v) BBr_3, CH_2Cl_2, 20 °C, 2−48 h; or PyHCl, 200 °C, 15 min.

Scheme 2[a]



[a] Reagents and conditions: (i) $Ph_3P{=}CHCO_2CH_2Ph$, CH_2Cl_2, 20 °C, 4 h; (ii) maleimide, 175 °C, 3 h; (iii) MnO_2, dioxane, reflux, 2 h; (iv) H_2/Pd−C, DMF−MeOH, 60 psi, 2 h; (v) DPPA, Et_3N, *t*-BuOH, reflux 16 h; then TFA, DCM, 20 °C, 1 h; (vi) aqueous H_2SO_4, $NaNO_2$, 3 °C, 3 min; then KI, CuI, 70 °C, 1 h; (vii) PyHCl, 200 °C, 15 min; (viii) $ArB(OH)_2$, catalyst $PdCl_2$(dppf), 2 N Na_2CO_3−dioxane, reflux 4 h.

kinase, another enzyme involved in regulation of the G2/M checkpoint.[12] In fact, inhibitors of Chk1 have also been proposed to sensitize cells to DNA-damaging agents in a manner similar to Wee1 inhibition.[13−15] While the dual Wee1/Chk1 inhibitory profile of this current series could ultimately prove to be advantageous, the initial goal of the present work was to prepare a series of selective Wee1 inhibitors so that their in vitro and in vivo effects could be evaluated in the absence of other confounding activities. The best DNA-damaging agent(s) for use in conjunction with a Wee1 inhibitor may well turn out to be different from those for use with a Chk1 inhibitor, and the optimum relative timing of administration of the checkpoint abrogator and DNA-damaging agent may not be the same for Wee1 and Chk1 inhibitors.

The synthesis of a series of related compounds lacking the 9-hydroxyl group as potential protein kinase C inhibitors has been reported,[16] but no biological data were provided.

In this paper we report on the synthesis and SAR of derivatives of **3**, defining structural features that are important for Wee1 activity and identifying substituents in the chromophore that lead to enhanced Wee1 potency and selectivity against Chk1. In particular, we report results from a comprehensive study of the effects of substitutions in the 4-phenyl ring on the activity of this novel class of Wee1 inhibitor.

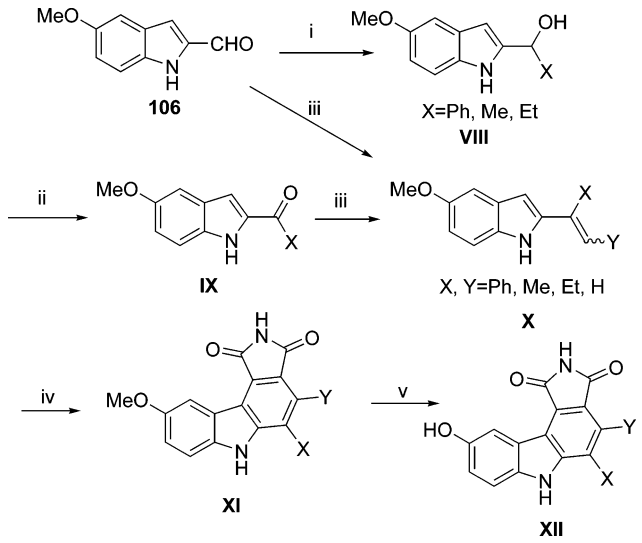
Chemistry

The 4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione ring system was built up as shown in Scheme 1. Substituted benzyltriphenylphosphonium halide salts were prepared from known substituted benzyl bromides (or benzyl alcohols following bromination) by reaction with triphenylphosphine. These were reacted in a Wittig condensation with indole-2-carboxaldehydes **I** to give dienes **II**, usually as an *E*/*Z* mixture of alkene isomers. This diene could be alkylated on the indole nitrogen to give **III**. A Diels−Alder reaction of the dienes **II** or **III** with maleimide was best performed as a neat melt at 175 °C or as a solution in refluxing toluene (with $SnCl_2$ catalyst) to give adduct **IV** as a mixture of diastereomers. Aromatization of **IV** was carried out using either excess activated MnO_2 or 2−5 equiv of DDQ to give **V**. This was demethylated to give the **VI** of Tables 1 and 2 using either pyridine hydrochloride at 200 °C or 2−10 equiv of BBr_3 in CH_2Cl_2 at room temperature. Analogous chemistry starting from a benzofuran-2-carboxaldehyde or a benzothiophene-2-carboxaldehyde gave the O- and S-analogues **8**, **9**, and **26** of Table 1. Additional examples of analogues substituted in the 4-phenyl ring, or with this ring replaced by a heterocycle, were prepared by efficient Suzuki coupling of the 4-iodide **5** with substituted arylboronic acids (Scheme 2). This final coupling step was also carried out in a parallel manner using commercially available boronic acids, which enabled a large number of compounds, **VII**, to be prepared. Wittig reaction of aldehyde **106** with benzyl (triphenylphosphoranylidene)acetate gave the *E*-diene **107** as the sole product. This reacted in a Diels−Alder reaction with maleimide at 175 °C to give **108**, which was aromatized and converted to the acid **110** in good yield. Curtius rearrangement of **110** gave amino compound **111**, which was converted into iodide **112** in a moderate yield of 46% via diazotization. Attempts to introduce a halogen substituent directly from **110** by halodecarboxylation[16] were unsuccessful.

Compounds containing amino functionality in the 4-phenyl ring were generally prepared by reduction of the corresponding nitro compounds, usually using nickel boride to preserve any halogen substituent also in this ring. Compounds containing 2′-methoxy substitution in the 4-phenyl ring could usually be selectively demethylated at the 9-methoxy group in the A-ring with BBr_3, leaving the former group intact. Under forcing conditions both methoxy groups were cleaved, generating hydroxy-substituted 4-phenyl groups.

The 2′-iodo and 2′-hydroxy compounds **29** and **38** were obtained via diazotization of the 9-methoxy derivative **139** of the amino compound **44**, followed by reaction with KI and CuI, which gave both a 2′-iodo and a 2′-hydroxyl derivative (**140** and **147**, respectively). Demethylation of these gave **29** and **38**, respectively. The primary amide **36** was prepared by partial

Scheme 3[a]



[a] Reagents and conditions: (i) XMgBr, THF, 0−20 °C, 50 min; (ii) MnO_2, $CHCl_3$, reflux, 40 min; (iii) $[PhCH_2PPh_3]Br$ or $[EtPPh_3]Br$ or $[MePPh_3]Br$, LDA, THF, reflux, 16 h (Y = Ph or Me or H, respectively); (iv) maleimide, 180 °C, 40 min, then MnO_2, dioxane, reflux, 4 h; (v) BBr_3, CH_2Cl_2, 20 °C, 3−8 h.

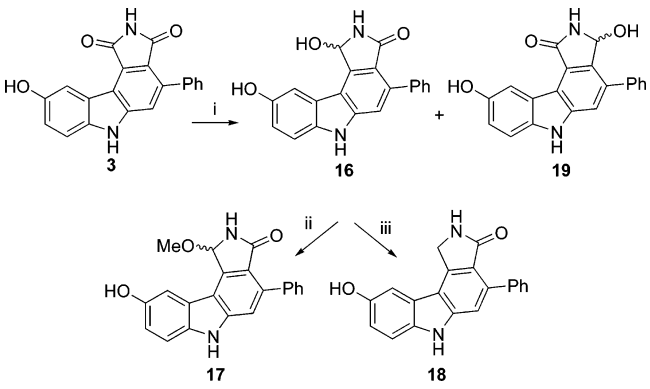
hydrolysis of the 9-methoxy derivative **143** of the nitrile **34** using H_2O_2 and K_2CO_3 in aqueous DMSO, which gave the primary amide but also converted the imide group to an anhydride **144**. Treatment of this material with an ammonium acetate melt to reform the imide ring followed by demethylation with BBr_3 gave **36**. The 2-phenyl derivative **37** was prepared via a Stille coupling on the 9-methoxy derivative **138** of the bromide **28** with tetraphenyltin, followed by demethylation. The sulfoxide **42** was obtained by oxidation of the thioether **41**. Saturated heterocycles **96** and **99** were obtained by hydrogenations of pyrrole **95** and pyridine **98**, respectively, over Adam's catalyst in the presence of hydrochloric acid. The N(2),N(6)-substituted analogue **20** was prepared by complete methylation of the parent **3** with MeI and NaH to give **133** followed by O-demethylation. The hydrazide **22** was prepared by reaction of **3** directly with hydrazine. Finally, the anhydride **21** was obtained as a hydrolysis byproduct during demethylation of the 9-methoxy derivative of **3**[11] with a pyridine hydrochloride melt.

Compounds containing functionality in the 5-position of the pyrrolocarbazole were prepared as shown in Scheme 3. The required 5-substituent was introduced via Grignard addition to 5-methoxyindole-2-carboxaldehyde **106**, followed by MnO_2 oxidation of the resulting alcohol **VIII** to give the ketone **IX**. Wittig reaction of **IX** using benzyl, ethyl, or methylphosphonium salts was used to introduce the 4-substituent (Ph, Me, or H), generating dienes **X**, which were elaborated to final products **XII** as described above.

Scheme 4 outlines the routes used to prepare derivatives with a reduced maleimide ring. Reduction of the lead molecule **3** with $NaBH_4$ gave the 1- and 3-hydroxy analogues **16** and **19** in a ratio of about 5:1, which were readily separable by chromatography on silica. Only one of the isomers displayed a strong nuclear Overhauser effect in its ^1H NMR spectrum between the H-10 proton and the hydroxyl doublet, and so this was assigned as structure **16**. Compounds **17** and **18** were prepared from **16** by standard methods as shown. Surprisingly the isomer **19** was completely unreactive under the same conditions and no derivatives of it could be prepared.

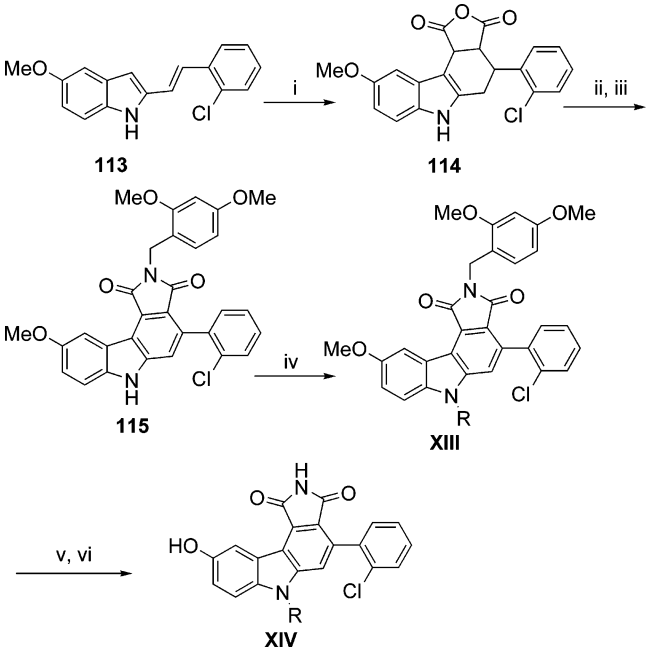
For the preparation of the compounds of Table 4 containing a range of functionality at the N6 position, an alternative route

Scheme 4[a]



[a] Reagents and conditions: (i) $NaBH_4$, EtOH, 20 °C, 18 h; (ii) TsOH, MeOH, 20 °C, 30 min; (iii) PhSeH, TsOH, THF, 20 °C, 1 h.

Scheme 5[a]



[a] Reagents and conditions: (i) maleic anhydride, xylene, reflux, 18 h; (ii) 2,4-dimethoxybenzylamine, AcOH, reflux, 6 h; (iii) MnO_2, dioxane, reflux, 16 h; (iv) RX, K_2CO_3, DMF, 90 °C, 3 h; (v) TFA, anisole, 90 °C, 18 h; (vi) BBr_3, CH_2Cl_2, 20 °C, 4 h.

was devised in which the maleimide nitrogen was protected with a 2,4-dimethoxybenzyl group, thereby enabling alkylation on the free N6-position to be carried out late in the synthesis (Scheme 5). Reaction of diene **113** with maleic anhydride gave anhydride **114**, which was reacted with 2,4-dimethoxybenzylamine and aromatized to give **115**. Alkylation of **115** on the N6 nitrogen proceeded in high yield to give **XIII**. Deprotection of the maleimide of **XIII** with trifluoroacetic acid/anisole followed by demethylation with BBr_3 then gave the final products **XIV**. This route enabled the introduction of a large number of substituents at the N6-position using parallel chemistry techniques.

Binding Mode of Pyrrolocarbazole 3

The mode of binding of the lead compound **3** in the ATP-binding site of Wee1 was initially predicted using a homology model of the enzyme, generated using the published crystal structures of the related kinase Chk1.[17,18] The model was subsequently fully validated when the structures of a cocrystal of **3** and a construct containing residues 291−575 of the human

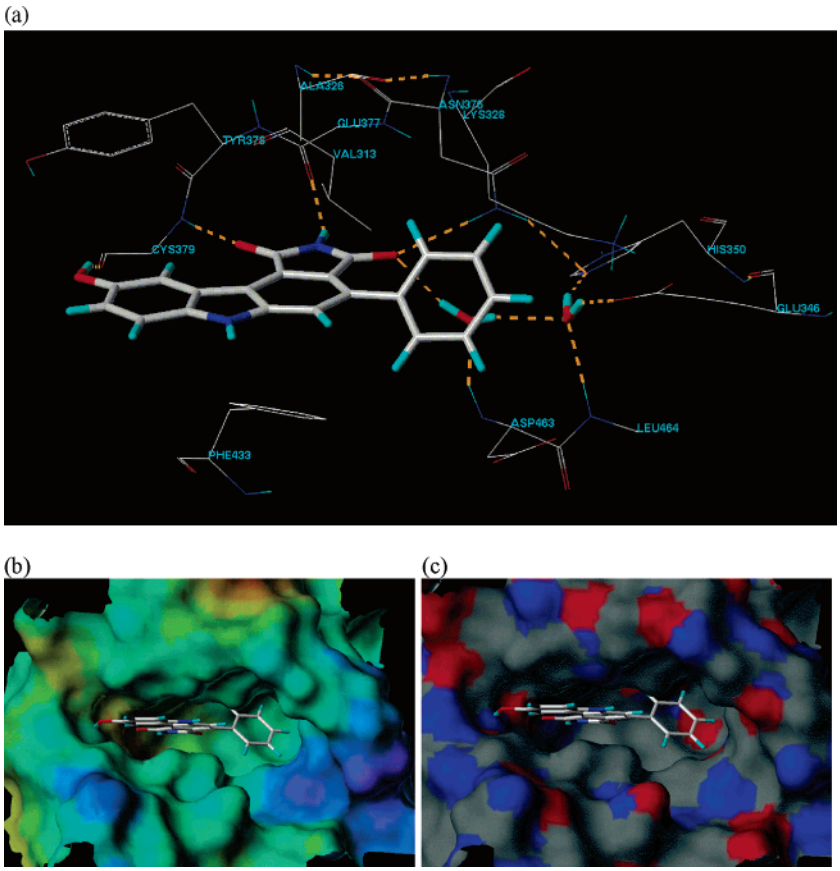


Figure 1. (a) Crystal structure of **3** bound in the ATP-binding site of a construct of Wee1 kinase. Coordinates used to generate the figure were taken from Squire et al.[19] and the PDB (code 1X8B). Important hydrogen bonds between the ligand, protein, and ordered water molecules in the active site are indicated with dotted orange lines. (b) ATP site color-coded by electrostatic potential. Blue areas are negatively charged, red areas denote positive charge, and neutral areas are in green and cyan. (c) ATP site color-coded by H-bonding regions. Red contains H-bonding donors in the protein, and blue contains H-bond acceptors.

Wee1 enzyme were solved to 1.8 Å resolution.[19] While this construct contained the substrate and ATP-binding sites of Wee1 and was thus useful for identifying the key features of ligand binding, it did not retain the full catalytic activity of the larger construct of Wee1 enzyme that was used in the IC_{50} enzyme measurements. On the other hand, this larger construct could not be induced to crystallize in a form that was suitable for crystallographic structure determinations.

The crystal structure provided additional information concerning the position of ordered water molecules in and around the active site and also identified a coordinated magnesium atom in this binding site. While several of these ordered water molecules were sufficiently close to the ligand to provide useful targets for drug improvement, the magnesium atom and its coordination sphere were not. Full details of the magnesium binding site can be found in the published crystal structure.[19] The pyrrolocarbazole binds with the pendant 4-phenyl ring twisted out of the plane of the chromophore and situated in the back of the ATP binding pocket (Figure 1). This phenyl binding pocket is rather hydrophobic, being bounded by the side chains of Val313, Lys328, and Ile374. Substituents placed on this ring would be expected to influence the specificity of binding to the Wee1 enzyme. The 9-hydroxyl group in the A-ring of the chromophore is placed at the entrance to the pocket and forms an H-bond contact with Cys379. The 1-carbonyl group accepts an H-bond from the same Cys379, and the 2-NH imide group donates an H-bond to Glu377. The 3-carbonyl group accepts an H-bond from both an ordered water and Asn376. Phe433 forms a π-stacking interaction with the B and C rings of the planar pyrrolocarbazole chromophore. There is room at the 6-position to accommodate moderately sized side chains, while side chains off the 8-position should protrude beyond the protein into solvent-accessible space.

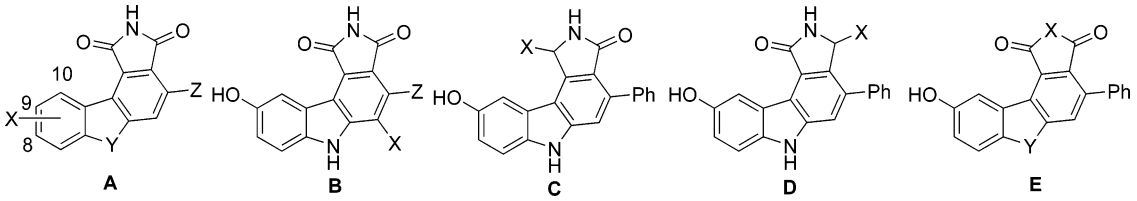
Results and Discussion

Compounds were evaluated for their ability to inhibit the incorporation of radiolabeled phosphate into a synthetic poly-ornithine−tyrosine peptide by a functional construct of human Wee1 kinase (aa 215−647). A similar assay was carried out against Chk1 kinase, using cdc25 as the enzyme substrate. Data from both assays are reported as the concentration of test compound required to inhibit phosphate incorporation by 50% (IC_{50}) in comparison to uninhibited controls and are determinations obtained from isolated enzymes. The final ATP concentration was 9.5 μM in the Wee1 assays and 4.0 μM in the Chk1 assays.

Initial SAR for Substitutions around the Pyrrolocarbazole Ring System. The compounds listed in Table 1 explored the preliminary SAR for potency and selectivity around the pyrrolocarbazole ring system. Removal of the 4-phenyl substituent (**4**), its replacement by iodine (**5**), or its movement to the 5-position (**15**) led to a significant loss in activity against Wee1, although Chk1 was more tolerant of these modifications, which therefore resulted in Chk1-selective compounds. Introduction of an adjacent methyl group at the 5-position (**11**) was tolerated by Wee1, but the larger 5-ethyl group (**12**) was not.

The combination of a 4-methyl and a 5-phenyl substituent (**13**) resulted in a potent, strongly Chk1-selective compound.

Table 1. Inhibitory Activity of Miscellaneous Pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione Derivatives



					IC$_{50}$ (μM)[a]			
compd	structure	X	Y	Z	Wee1	Chk1	ratio[b]	synthetic route[c]
3	**A**	9-OH	NH	Ph	0.097	0.047	0.48	1[d]
4	**A**	9-OH	NH	H	4.0	0.47	0.12	3
5	**A**	9-OH	NH	I	2.3	0.038	0.017	2
6	**A**	8-OH	NH	Ph	0.31	0.30	0.97	1
7	**A**	10-OH	NH	Ph	>50	>10		1
8	**A**	9-OH	O	Ph	0.43	>10	>23	1
9	**A**	9-OH	S	Ph	0.078	0.21	2.7	1
10	**A**	9-OH	NMe	Ph	0.26	0.056	0.22	1
11	**B**	Me		Ph	0.13	0.24	1.8	3
12	**B**	Et		Ph	1.6	0.43	0.27	3
13	**B**	Ph		Me	9.7	0.032	0.003	3
14	**B**	Ph		Ph	2.3	0.37	0.16	3
15	**B**	Ph		H	4.0	0.33	0.082	3
16	**C**	OH			>50	>10		4
17	**C**	OMe			20	>10		4
18	**C**	H			37	>10		4
19	**D**	OH			2.8	0.074	0.026	4
20	**E**	NMe	NMe		>50	>10		special[e]
21	**E**	O	NH		>50	4.6	<0.09	special[e]
22	**E**	N−NH$_2$	NH		3.9	5.8	1.5	special[e]
23	**A**	9-OH	NH	2-ClPh	0.011	0.44	40	2
24	**A**	9-OMe	NH	2-ClPh	0.64	3.2	5.0	1
25	**A**	9-OH	NMe	2-ClPh	0.057	0.22	3.9	5A
26	**A**	9-OH	O	2-ClPh	0.033	>10	>303	1

[a] IC$_{50}$ values against the isolated enzyme are the average of at least three individual determinations. Replicate values were within 30% of each other. [b] Ratio of Chk1 IC$_{50}$ to Wee1 IC$_{50}$. [c] Scheme number used for synthesis. [d] Reference 11. [e] See Experimental Section for details.

Methylation of the 9-hydroxyl group (**24**) or its movement to the adjacent 10-position (**7**) significantly reduced activity against both Wee1 and Chk1, while its movement to the 8-position (**6**) led to a 3- to 6-fold loss in potency against both enzymes. Activity was also significantly reduced when the 1-carbonyl group was modified (**16**−**18**), whereas reduction of the 3-carbonyl group (**19**) was somewhat better tolerated, particularly by Chk1. A free NH at the 2-position of the maleimide ring was important for activity against both Wee1 and Chk1 (**20**−**22**), with N-methylation of this group (compare **20** with **10**) leading to a >100-fold loss in potency.

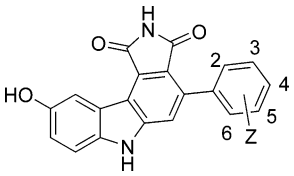
These SARs are largely consistent with the observed binding mode (see above), where loss of any of the key H-bond contacts between the ligand and protein leads to a loss in Wee1 activity. An exception was the relatively modest (3-fold) loss in Wee1 potency upon movement of the 9-hydroxyl group to the adjacent 8-position. The X-ray crystal structure of a Wee1 construct with inhibitor **3** bound in the active site[19] reveals a network of three ordered water molecules close to the 8-position of the pyrrolocarbazole ring system, and it is possible that the 8-hydroxyl group of **6** forms a stabilizing H-bond with one of these.

A comparison of **3** with **8**−**10** and **25** showed that the carbazole N6 nitrogen could be alkylated or replaced by O or S, with retention of significant Wee1 activity. The oxygen analogue **8** displayed significantly improved Wee1 selectivity when compared with the lead **3**, with only a 4-fold loss in Wee1 potency. This trend was mirrored in the more potent series containing a 2-chlorophenyl substituent at the 4-position, with dibenzofuran **26** displaying an impressive >300-fold selectivity for Wee1. Comparisons of the pairs **3**/**23**, **10**/**25**, and **8**/**26** showed that a 2-chloro substituent on the phenyl ring increased potency against Wee1 by about 10-fold (see later), with compound **23** in particular displaying excellent Wee1 potency (IC$_{50}$ = 11 nM). A 2′-chloro substituent was similarly observed to increase Wee1 potency in the 6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one series of Wee1 inhibitors[7] (e.g., **1**, **2**), suggesting that the pendant 6-phenyl ring occupies a similar binding site in the protein compared to the 4-phenyl ring of the pyrrolocarbazoles. As expected from the above data sets, there was no overall correlation between Wee1 and Chk1 potencies for this diverse set of analogues.

SAR for Substitution in the 4-Phenyl Ring. Because of the increase in potency achieved by introduction of a 2′-Cl substituent, we carried out a more general evaluation of the effects of substitution in the 4-phenyl ring on the activity of the 9-hydroxy-4-phenylpyrrolocarbazoles as inhibitors of Wee1 and Chk1 kinases. Table 2 lists data for 67 4-phenyl-substituted analogues.

Compounds **23** and **27**−**44** are 2′-monosubstituted. Lipophilic 2′-substituents such as Cl, Br, I, OMe, and SMe did improve Wee1 potency, while Me, OH, and NO$_2$ substitution provided compounds almost equipotent with the unsubstituted compound **3**. Other 2-substituents, including the bulky phenyl group (**37**), were generally tolerated by Wee1, with only a slight loss in potency. In contrast, Chk1 was generally much less tolerant of 2′-substitution, with the result that selectivity for Wee1 was raised from 0.48-fold for **3** to typically 10- to 100-fold. Compounds **41** and **42** (2′-SMe and 2′-SOMe) displayed remarkable Wee1 selectivity (>1500-fold and >225-fold, respectively). Substitution at the 2′-position of the 4-phenyl ring would have the greatest effect on twisting this ring out of the plane of the carbazole ring system, leading to more favorable interactions between this ring and the protein. This 2′-substituent

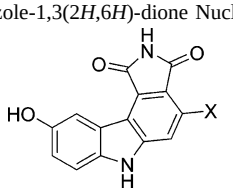
Table 2. Inhibitory Activity of Substituted 4-Phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione Derivatives



compd	Z	IC$_{50}$ (μM)[a] Wee1	Chk1	ratio[b]	synthetic route[c]
3	H	0.097	0.047	0.48	1[d]
27	2-F	0.33	0.077	0.23	2A[e]
23	2-Cl	0.011	0.44	40	2
28	2-Br	0.023	0.15	6.5	1
29	2-I	0.013	0.62	48	special[f]
30	2-Me	0.15	0.30	2.0	2A[e]
31	2-Et	0.51	19	37	2
32	2-CF_3	0.58	10	17	2
33	2-CH_2OH	0.45	0.45	1.0	2
34	2-CN	0.19	0.032	0.17	1
35	2-COMe	0.83	0.11	0.13	2A[e]
36	2-$CONH_2$	0.16	2.4	15	special[f]
37	2-Ph	0.57	0.21	0.37	special[f]
38	2-OH	0.060	1.2	20	special[f]
39	2-OMe	0.024	0.50	21	2
40	2-OEt	0.26	3.8	15	2
41	2-SMe	0.033	>50	>1500	2
42	2-SOMe	0.22	>50	>225	from **41**
43	2-NO_2	0.047	4.0	85	1
44	2-NH_2	0.21	0.79	3.8	from **43**
45	3-F	0.22	0.073	0.33	2A[e]
46	3-Cl	0.055	0.33	6	2A[e]
47	3-Me	0.23	0.62	2.7	2A[e]
48	3-CF_3	>50	>10		2A[e]
49	3-CH_2OH	0.87	0.97	1.1	2A[e]
50	3-CH_2NH_2	4.4	23	5.2	2
51	3-CN	0.18	4.2	23	2A[e]
52	3-COMe	4.3	>10	>2.3	2A[e]
53	3-Ph	40	44	1.1	2
54	3-OH	0.089	0.26	2.9	from **55**
55	3-OMe	0.62	2.2	3.5	2A[e]
56	3-NO_2	0.30	>10	>33	1
57	3-NH_2	0.070	1.6	23	2
58	4-F	16	2.8	0.18	2A[e]
59	4-Cl	0.73	>10	>14	2A[e]
60	4-Me	3.3	2.8	0.85	2A[e]
61	4-CF_3	>50	>10		2A[e]
62	4-CH_2OH	1.2	0.34	0.28	2
63	4-CN	1.8	0.12	0.07	2A[e]
64	4-COMe	3.6	>10	>2.8	2
65	4-OH	0.067	0.021	0.31	from **66**
66	4-OMe	12	1.3	0.11	2A[e]
67	4-SMe	29	>10	>0.35	2A[e]
68	4-SO_2Me	1.1	10	9.1	2A[e]
69	4-NH_2	0.15	0.021	0.14	2
70	2-Cl, 3-Cl	0.028	0.24	8.6	2
71	2-Cl, 3-OH	0.012	0.97	81	1
72	2-Cl, 3-NH_2	0.021	0.48	23	1
73	2-Cl, 4-OH	0.023	0.13	5.6	1
74	2-Cl, 4-NH_2	0.024	0.23	9.6	1
75	2-Cl, 5-Cl	0.49	>10	>20	2A[e]
76	2-Cl, 5-OH	0.042	1.1	26	1
77	2-Cl, 5-NH_2	0.020	5.3	265	1
78	2-Cl, 6-Cl	0.028	1.2	43	1
79	2-Cl, 6-OH	0.045	0.79	18	from **80**
80	2-Cl, 6-OMe	0.015	0.60	40	2A
81	2-Br, 4-NH_2	0.020	0.22	11	1
82	2-Br, 6-Br	0.035	7.0	200	1
83	2-Me, 3-Me	0.27	7.1	26	2A[e]
84	2-Me, 5-Me	0.96	>10	>10	2A[e]
85	2-Me, 6-Me	0.075	>10	>133	2
86	2-OMe, 4-NH_2	0.019	4.7	247	1
87	2-OMe, 5-NH_2	0.11	>10	>91	1
88	2-OMe, 6-OMe	0.027	5.3	196	2
89	2-OMe, 6-F	0.029	0.71	24	2
90	2,6-diCl, 3-OH	0.018	2.4	133	1
91	2,6-diCl, 4-OH	0.049	1.3	26	1

[a] IC$_{50}$ values against the isolated enzyme are the average of at least three individual determinations. Replicate values were within 30% of each other. [b] Ratio of Chk1 IC$_{50}$ to Wee1 IC$_{50}$. [c] Scheme number used for synthesis. [d] Reference 11. [e] Letter A indicates that array synthesis was used; see Experimental Section for details. [f] See Experimental Section for details.

Table 3. Effect of Heterocyclic Ring Substitution at the 4-Position of the Pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione Nucleus



No	X	IC$_{50}$ (μM)[a] Wee1	Chk1	Ratio[b]	Synthetic Route[c]
92		0.14	0.12	0.86	2
93		0.042	0.017	0.40	2
94		0.18	0.16	0.89	2
95		0.038	0.026	0.68	2
96		13	24	1.8	From **95**
97		0.82	0.31	0.38	2
98		0.58	2.3	4.0	2
99		10	>50	>5	From **98**

[a] IC$_{50}$ values against the isolated enzyme are the average of at least three individual determinations. Replicate values were within 30% of each other. [b] Ratio of Chk1 IC$_{50}$ to Wee1 IC$_{50}$. [c] Scheme number used for synthesis.

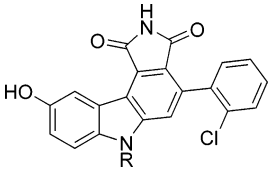
would occupy a moderately lipophilic binding pocket in Wee1 bounded by Val313, Ala326, and Lys328.

Compounds **45**−**57** are 3′-monosubstituted. The same broad overall SARs were followed, in that small groups were generally acceptable, although in this case they provided very little improvement in Wee1 potency over **3** and smaller increases in Wee1/Chk1 selectivity (generally 3- to 6-fold). Larger groups such as phenyl were poorly tolerated. Compounds **58**−**69** are 4′-monosubstituted. Polar, H-bond donating 4′-substituents (e.g., OH, NH_2) were well tolerated by both enzymes, resulting in no overall change in selectivity profile, but most other substitutions resulted in a >10-fold loss in potency.

Compounds **70**−**80** combine a 2′-Cl group with various 3′-, 4′-, 5′-, or 6′-substituents. Generally, these compounds retained both the high Wee1 potency (many between 10 and 30 nM) and the high Wee1/Chk1 selectivity displayed by the 2′-chloro compound **23**. The 2′-Cl, 4′-OH and 2′-Cl, 4′-NH_2 compounds **73** and **74** are interesting, showing substantially lower Chk1 activity than the corresponding 4′-OH and 4′-NH_2 compounds **65** and **69**, respectively. Similar results were seen for the comparable 2′-Br and 2′-OMe analogues **81** and **86**, which show excellent selectivity due to low Chk1 activity. Addition of a 5′-amino substituent to the 2′-chloro or 2′-methoxyphenyl ring (**77** and **87**) also resulted in improved Wee1 selectivity, with good potency being retained in the former case. The 2′,6′-Cl, 2′,6′-Br, and 2′,6′-diOMe compounds **78**, **82**, and **88** also showed excellent Wee1 potency and selectivity, with the 2′,6′-diMe analogue **85** being slightly less potent but also highly selective.

Heterocycles off the 4-Position. A series of compounds were evaluated in which the 4-phenyl substituent was replaced with a heterocyclic ring (Table 3). Incorporation of a thienyl or a

Table 4. Effect of Steric Bulk at the N6 Position of 4-(2′-Chlorophenyl)pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione Derivatives



		IC_{50} (μM)[a]			
compd	R	Wee1	Chk1	ratio[b]	synthetic route[c]
25	Me	0.057	0.22	3.9	5A
100	Et	0.050	0.12	2.4	5A
101	*n*-Pr	0.063	0.45	7.1	5A
102	*i*-Pr	0.053	27	509	5A
103	*n*-Bu	0.059	35	593	5A
104	$(CH_2)_2$*i*-Pr	0.15	24	160	5A
105	*n*-pent	0.17	44	259	5A

[a] IC_{50} values against the isolated enzyme are the average of at least three individual determinations. Replicate values were within 30% of each other. [b] Ratio of Chk1 IC_{50} to Wee1 IC_{50}. [c] Scheme number used for synthesis. The letter A indicates that array synthesis was used; see Experimental Section for details.

pyrrole ring gave compounds with comparable Wee1 and Chk1 potencies to the phenyl compound, with the 3′-substituted derivatives **93** and **95** displaying better activities than their 2′-substituted analogues (**92** and **94**). 4-Pyridyl-substituted compounds **97** and **98** were somewhat less active. The reduced derivatives **96** and **99** of the 3-pyrrole and 3-pyridyl compounds **95** and **98** were much less potent, suggesting either loss of a favorable π-interaction with the protein or low tolerance for a more basic nitrogen atom in the active site. If this basic nitrogen is charged on binding, its presence would likely disfavor ligand binding in the rather lipophilic Wee1 binding site. None of these heterocyclic derivatives displayed significantly improved selectivity for Wee1 compared with 4-phenyl-substituted compounds.

SAR for N6 Substitution. In deciding on suitable 4-phenyl substituents for exploring SAR at other points on the molecule, Wee1 potency, Wee1/Chk1 selectivity, ease of synthesis and potential compound metabolic stability were considered. For these reasons, a 2′-Cl substituent was chosen to explore the SAR for N6 substitution, as shown in Table 4. Compounds **25** and **100**−**105** were explored for nonpolar substituents off the N6 position. These analogues showed little change in potency for Wee1 but a marked increase in selectivity due to a drop-off in Chk1 inhibition for the *i*-Pr and longer-chain derivatives, suggesting less bulk tolerance at this position in the Chk1 ATP binding site. Indeed, Chk1 has a bulky Glu91 protruding into this region of the protein, whereas Wee1 has the smaller and less polar Ser383.

Conclusions

While the lead 4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione **3** was a potent but nonselective inhibitor of Wee1 versus Chk1 kinase, good selectivity for Wee1 could be achieved by the introduction of lipophilic functionality at the 2′-position and the 2′,6′-positions of the 4-phenyl ring. Enhanced Wee1 selectivity was also observed from substitution of the phenyl ring with a 2′-lipophilic group together with a 5′-NH_2 group and by incorporation of moderate steric bulk off the N6-position. Replacement of the N6 atom by oxygen to give the dibenzofuran analogue of the carbazole also resulted in Wee1-selective inhibition. Key features of the binding mode for this class of inhibitor were previously determined by X-ray crystallography of a cocrystal of an inhibitor bound in a construct of the enzyme, and the SARs seen here are broadly consistent with this binding mode. Although some of these compounds are potent and selective inhibitors of the Wee1 enzyme, they have low aqueous solubilities (typically less than 3 μg/mL) and low permeabilities across Caco-2 cell monolayers ($P_{app} < 3 \times 10^{-6}$ cm/s). This has precluded us from obtaining meaningful data on the effects of these compounds on abrogation of the G2/M checkpoint in whole cells. Nevertheless, the results show that 4-phenylpyrrolo-[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione is a suitable molecular framework on which to elaborate analogues with solubilizing substituents at defined positions, especially N6 and C8, guided by ongoing crystallographic analysis and molecular modeling. These studies will be reported subsequently.

Experimental Section

Combustion analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined using an Electrothermal model 9200 digital melting point apparatus and are as read. NMR spectra were measured on a Bruker DRX-400 spectrometer or a Bruker Avance-400 spectrometer and are referenced to Me_4Si. High-resolution mass spectra were recorded on a Varian VG-70SE spectrometer at nominal 5000 resolution. Liquid chromatography−mass spectrometry (LC−MS) was performed on an Agilent 1100 LC system interfaced with an Agilent MSD mass detector. Mass detection was performed with an APCI source, using simultaneous positive and negative ion acquisition. Compound purities were determined by HPLC using simultaneous diode array UV detection. Unless otherwise indicated, compounds were purified by flash column chromatography on silica gel 60 support (Scharlau, 230−400 mesh ASTM), using the indicated eluants.

Procedures of Scheme 1. Procedure 1. (2,6-Dichlorobenzyl)-(triphenyl)phosphonium Bromide (116). A mixture of 2,6-dichlorotoluene (20.1 g, 0.125 mol), *N*-bromosuccinimide (24.6 g, 0.138 mol), and 2,2′-azobisisobutyronitrile (0.41 g, 2.50 mmol) in dry benzene (300 mL) under N_2 was stirred at reflux for 6 h with continuous irradiation from a 100 W lamp. The resulting reaction mixture was concentrated under vacuum (to 50 mL), cooled, filtered, and washed with dry benzene. The filtrate (containing the crude benzyl bromide) was treated directly with triphenylphosphine (49.3 g, 0.188 mol) and was stirred at reflux for 17 h. After the mixture was cooled, the precipitate was collected by filtration, washed thoroughly with dry benzene and then pentane, and dried under vacuum at 50 °C to give **116** (62.1 g, 99%) as a cream powder. An analytical sample was obtained by recrystallization: mp (CH_2Cl_2/benzene) 269−272 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (m, 9 H), 7.64 (m, 6 H), 7.18 (s, 3 H), 5.50 (d, J = 14.3 Hz, 2 H). Anal. ($C_{25}H_{20}BrCl_2P$) C, H.

Procedure 2. 2-[(*E*)-2-(2,6-Dichlorophenyl)ethenyl]-5-methoxy-1*H*-indole (117). Lithium diisopropylamide (52 mL of a 1.5 M solution in cyclohexane, 78 mmol) was added dropwise to a stirred suspension of **116** (34.6 g, 68.9 mmol) in dry THF (100 mL) under N_2 at 0 °C, and then the mixture was stirred at room temperature for 45 min and then at 50 °C for 30 min, then cooled to 0 °C. A solution of 5-methoxy-1*H*-indole-2-carbaldehyde[20,21] (**106**) (10.0 g, 57.1 mmol) in dry THF (60 mL, then 2 × 10 mL to rinse) was added, and the mixture was stirred at reflux for 5 h. The cooled solution was added to a mixture of ice and aqueous sodium bicarbonate (200 mL), the organic layer was separated, and the aqueous portion was further extracted with CH_2Cl_2 (5 × 150 mL). The combined organics were washed with water (2 × 200 mL), back-extracted with CH_2Cl_2 (2 × 100 mL), and evaporated to dryness. Then the residue was chromatographed on silica gel. Elution with 0−40% CH_2Cl_2/light petroleum gave foreruns. Then further elution with 50% CH_2Cl_2/light petroleum to 100% CH_2Cl_2 gave pure *E* diene **117** (**II**, 5-OMe, Ar = 2,6-dichlorophenyl) (17.6 g, 97%) as a yellow solid following recrystallization: mp (CH_2Cl_2/hexane) 144−147 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1 H), 7.36 (d, J = 8.1 Hz, 1 H), 7.27 (m, 1 H), 7.25 (d, J = 16.8 Hz, 1

H), 7.11 (t, $J = 8.0$ Hz, 1 H), 7.03 (d, $J = 2.4$ Hz, 1 H), 6.93 (d, $J = 16.8$ Hz, 1 H), 6.88 (dd, $J = 8.7$, 2.5 Hz, 1 H), 6.61 (d, $J = 1.8$ Hz, 1 H), 3.86 (s, 3 H). Anal. ($C_{17}H_{13}Cl_2NO$) C, H, N.

Procedure 3. 4-(2,6-Dichlorophenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (118). A mixture of pure *E* diene **117** (1.51 g, 4.73 mmol), maleimide (1.90 g, 19.6 mmol), and powdered $SnCl_2$ (67 mg, 0.35 mmol) in toluene (20 mL) was stirred in a foil-covered sealed vial at 125 °C for 3 h. The cooled solution was added to aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (7 × 100 mL). The combined extracts were evaporated to dryness to give a crude adduct (**IV**, 9-OMe, R = H, Ar = 2,6-dichlorophenyl) as a tan powder, which was used directly.

Procedure 4. The crude Diels−Alder adduct above was reacted directly with DDQ (5.44 g, 24.0 mmol) in toluene (60 mL) and dioxane (60 mL), stirring at reflux for 2 days. The cooled solution (and precipitated solids after dissolving these in $CHCl_3$) was sequentially washed twice with aqueous sodium bicarbonate (300 mL, then 150 mL) and water (2 × 150 mL). Then the aqueous washings were back-extracted with $CHCl_3$ (8 × 150 mL), washing these extracts in the same way. The combined organics were evaporated to dryness, and then the residue was chromatographed on silica gel. Elution with 0−0.5% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 0.5% MeOH/CH_2Cl_2 gave **118** (**V**, 9-OMe, R = H, Ar = 2,6-dichlorophenyl) (1.52 g, 78%) as a yellow solid following recrystallization: mp (MeOH/CH_2Cl_2/hexane) 299−301 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.02 (br s, 1 H), 11.15 (br s, 1 H), 8.45 (d, $J = 2.6$ Hz, 1 H), 7.61 (d, $J = 7.7$ Hz, 2 H), 7.61 (s, 1 H), 7.59 (d, $J = 8.9$ Hz, 1 H), 7.50 (dd, $J = 8.8$, 7.4 Hz, 1 H), 7.26 (dd, $J = 8.9$, 2.7 Hz, 1 H), 3.90 (s, 3 H). Anal. ($C_{21}H_{12}Cl_2N_2O_3$) C, H, N.

Procedure 5. 4-(2,6-Dichlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (78). Boron tribromide (18.5 mL of a 1.0 M solution in CH_2Cl_2, 18.5 mmol) was added to a stirred solution of carbazole methyl ether **118** (1.52 g, 3.70 mmol) in dry CH_2Cl_2 (100 mL) under N_2 at 0 °C, and then the mixture was stirred at room temperature for 2.5 h. The resulting solution was added to a mixture of ice and aqueous sodium bicarbonate (300 mL) and extracted with EtOAc (5 × 200 mL). The combined extracts were washed with water (200 mL) and evaporated to dryness, and then the residue was chromatographed on silica gel. Elution with 0−2% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 2−3% MeOH/CH_2Cl_2 gave phenol **78** (1.45 g, 97%) as an orange solid following recrystallization: mp (MeOH/CH_2Cl_2/hexane) 205−215 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.89 (br s, 1 H), 11.08 (br s, 1 H), 9.32 (br s, 1 H), 8.30 (d, $J = 2.4$ Hz, 1 H), 7.61 (d, $J = 7.9$ Hz, 2 H), 7.55 (s, 1 H), 7.50 (dd, $J = 8.7$, 7.4 Hz, 1 H), 7.47 (d, $J = 8.7$ Hz, 1 H), 7.10 (dd, $J = 8.7$, 2.4 Hz, 1 H). Anal. ($C_{20}H_{10}Cl_2N_2O_3 \cdot 0.5H_2O$) C, H, N.

8-Methoxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (122). Reaction of 6-methoxyindole-2-carboxaldehyde[22] (**119**) (**I**, 6-OMe) with benzyltriphenylphosphonium bromide using procedure 2 gave 6-methoxy-2-[2-phenylethenyl]-1*H*-indole (**120**) (**II**, 6-OMe, Ar = phenyl) (94%) as a white solid (mixture of *E/Z* isomers), which was used without further purification.

Reaction of the diene **120** with maleimide using procedure 3 gave 8-methoxy-4-phenyl-4,5,6,10c-tetrahydropyrrolo[3,4-*c*]carbazole-1,3(2*H*,3a*H*)-dione (**121**) (**IV**, 8-OMe, R = H, Ar = phenyl) (61%) as a tan solid, which was used without further purification.

Aromatization of **121** with DDQ using procedure 4 gave **122** (**V**, 8-OMe, R = H, Ar = phenyl) (65%) as a yellow powder: mp 154−156 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.87 (br, 1H), 11.02 (br, 1H), 8.75 (d, $J = 8.8$ Hz, 1H), 7.61 (dd, $J = 8.0$, 1.8 Hz, 2H), 7.60 (s, 1H), 7.49−7.40 (m, 3H), 7.10 (d, $J = 2.2$ Hz, 1H), 6.94 (dd, $J = 8.8$, 2.2 Hz, 1H), 3.90 (s, 3H). Anal. ($C_{21}H_{14}N_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

8-Hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (6). Demethylation of **122** with BBr_3 using procedure 5 gave **6** as a yellow powder (74%): mp >330 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.75 (br, 1H), 10.96 (br, 1H), 10.56 (br, 1H), 8.66 (d, $J = 8.6$ Hz, 1H), 7.60 (dd, $J = 8.0$, 1.8 Hz, 2H), 7.53 (s, 1H), 7.49−7.39 (m, 3H), 6.93 (d, $J = 2.1$ Hz, 1H), 6.79 (dd, $J = 8.6$, 2.1 Hz, 1H). Anal. ($C_{20}H_{12}N_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

10-Methoxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (126). Reaction of 4-methoxyindole-2-carboxaldehyde[23] (**123**) (**I**, 4-OMe) with benzyltriphenylphosphonium bromide using procedure 2 gave 4-methoxy-2-[2-phenylethenyl]-1*H*-indole (**124**) (**II**, 4-OMe, Ar = phenyl) (89%) as a fluorescent oil (mixture of *E/Z* isomers), which was used without further purification.

Reaction of the diene **124** with maleimide using procedure 3 gave 10-methoxy-4-phenyl-4,5,6,10c-tetrahydropyrrolo[3,4-*c*]carbazole-1,3(2*H*,3a*H*)-dione (**125**) (**IV**, 10-OMe, R = H, Ar = phenyl) (86%) as a yellow solid, which was used without further purification.

Aromatization of **125** with DDQ using procedure 4 gave **126** (**V**, 10-OMe, R = H, Ar = phenyl) (78%) as yellow needles: mp 273−276 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.10 (s, 1H), 10.78 (s, 1H), 7.59 (s, 1H), 7.57 (dd, $J = 8.0$, 1.8 Hz, 2H), 7.49 (t, $J = 7.9$ Hz, 1H), 7.47−7.39 (m, 3H), 7.16 (d, $J = 7.9$ Hz, 1H), 6.80 (d, $J = 7.9$ Hz, 1H), 3.99 (s, 3H). Anal. ($C_{21}H_{14}N_2O_3$) C, H, N.

10-Hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (7). Demethylation of **126** with BBr_3 using procedure 5 gave **7** as a yellow-orange solid (92%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.33 (s, 1H), 12.16 (s, 1H), 11.65 (br, 1H), 7.62 (s, 1H), 7.60 (dd, $J = 7.9$, 1.8 Hz, 2H), 7.51−7.45 (m, 3H), 7.40 (dd, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 7.6$ Hz, 1H), 6.63 (d, $J = 7.6$ Hz, 1H). Anal. ($C_{20}H_{12}N_2O_3$) C, H, N.

5-Methoxy-2-[(*E,Z*)-2-phenylethenyl]-1-benzofuran (127). A suspension of benzyltriphenylphosphonium bromide (1.85 g, 4.26 mmol) in THF (30 mL) was treated with a solution of lithium bis(trimethylsilyl)amide (4 mL of a 1 M solution in THF, 3.98 mmol). The reaction mixture was stirred at room temperature for 30 min, and then a solution of 5-methoxy-1-benzofuran-2-carbaldehyde[24] (0.50 g, 2.84 mmol) in THF (10 mL) was added. After 20 min water was added and the THF was removed at reduced pressure. The residue was extracted with EtOAc (2 × 50 mL), and the combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel, eluting with DCM to give **127** as a 1:2 mixture of *Z*- and *E*-isomers, which was used directly (0.63 g, 89%): mp 124−128 °C. Anal. ($C_{17}H_{14}O_2$) C, H.

9-Methoxy-4-phenyl-1*H*-[1]benzofuro[3,2-*e*]isoindole-1,3(2*H*)-dione (128). The diene mixture **127** was reacted with maleimide using procedure 3 and then aromatized with MnO_2 using procedure 7 to give **128** as a yellow solid (53%): mp 271−275 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (br s, 1H), 8.24 (d, $J = 2.7$ Hz, 1H), 7.98 (s, 1H), 7.77 (d, $J = 9.0$ Hz, 1H), 7.67−7.65 (m, 2H), 7.51−7.45 (m, 3H), 7.30 (dd, $J = 9.0$, 2.7 Hz, 1H), 3.91 (s, 3H). Anal. ($C_{21}H_{13}NO_4 \cdot {}^1/_3H_2O$) C, H, N.

9-Hydroxy-4-phenyl-1*H*-[1]benzofuro[3,2-*e*]isoindole-1,3(2*H*)-dione (8). Demethylation of **128** with BBr_3 using procedure 5 gave **8** (100%): mp 288−290 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.37 (br s, 1H), 9.74 (s, 1H), 8.13 (d, $J = 2.6$ Hz, 1H), 7.94 (s, 1H), 7.66−7.63 (m, 3H), 7.51−7.44 (m, 3H), 7.11 (dd, $J = 8.9$, 2.6 Hz, 1H). Anal. ($C_{20}H_{11}NO_4 \cdot {}^1/_2H_2O$) C, H, N.

9-Hydroxy-4-phenyl-1*H*-[1]benzothieno[3,2-*e*]isoindole-1,3-(2*H*)-dione (9). Reaction of 5-methoxy-1-benzothiophene-2-carbaldehyde[25] with benzyltriphenylphosphonium chloride using procedure 2 gave 5-methoxy-2-[(*E,Z*)-2-phenylethenyl]-1-benzothiophene (**129**) as an *E/Z* mixture (63%): ^{1}H NMR ($CDCl_3$) minor isomer δ 7.60 (d, 1H), 7.40 (m, 5H), 7.15 (s, 1H), 7.05 (s, 1H), 6.91 (d, 1H), 6.75 (m, 2H), 3.85 (s, 3H); ^{1}H NMR ($CDCl_3$) major isomer δ 7.75 (d, $J = 9$ Hz, 1H), 7.55 (m, 2H), 7.25−7.4 (m, 3H), 7.18 (m, 2H), 7.05 (s, 1H), 6.95 (m, 2H), 3.86 (s, 3H).

Reaction of **129** with maleimide for 6 days using procedure 3, followed by aromatization with MnO_2 in $CHCl_3$ for 5 days at 40 °C following procedure 7, gave 9-methoxy-4-phenyl-1*H*-[1]benzothieno[3,2-*e*]isoindole-1,3(2*H*)-dione (**130**) (44%): ^{1}H NMR [$(CD_3)_2SO$] δ 11.46 (s, 1H), 9.37 (d, $J = 2.5$ Hz, 1H), 8.38 (s, 1H), 8.2 (d, $J = 9$ Hz, 1H), 7.62 (m, 2H), 7.48 (m, 3H), 7.31 (dd, $J = 2.5$, 9.0 Hz, 1H), 3.94 (s, 3H).

Demethylation of **130** with BBr_3 for 48 h using procedure 5 gave **9** (65%): mp 311−313 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.42 (s, 1H),

9.85 (s, 1H), 9.17 (d, J = 2.5 Hz, 1H), 8.32 (s, 1H), 7.9 (d, J = 9 Hz, 1H), 7.62 (m, 2H), 7.5 (m, 3H), 7.17 (dd, J = 2.5, 9 Hz, 1H). Anal. ($C_{20}H_{11}NO_3S \cdot 0.2H_2O$) C, H, N, S.

9-Methoxy-6-methyl-4-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (132). To a stirred solution of 2-[2-phenylethenyl]-5-methoxy-1*H*-indole[11] (**131**) (**II**, 5-OMe, Ar = phenyl) (0.20 g, 0.80 mmol) in DMF (5 mL) under nitrogen was added sodium hydride (91 mg of a 50% dispersion in oil, 1.9 mmol) followed by methyl iodide (0.041 mL, 0.71 mmol). After 15 min the reaction mixture was diluted with water and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was then dissolved in toluene (20 mL), and maleimide (92 mg, 0.95 mmol) was added before the solution was heated at reflux for 24 h and the reaction mixture was concentrated to dryness. The product was redissolved in dioxane (100 mL) before activated MnO_2 (1.24 g, 14.25 mmol) was added, and the resulting suspension was heated at reflux for 18 h. Filtration through Celite, concentration under reduced pressure, and chromatography on silica, eluting with ethyl acetate/dichloromethane (1:3), followed by trituration from methanol, gave **132** (**V**, 9-OMe, R = Me, Ar = phenyl) (0.20 g, 70%) as a yellow powder: mp 286−291 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.11 (br s, 1H), 8.53 (d, J = 2.6 Hz, 1H), 7.80 (s, 1H), 7.66 (m, 3H), 7.47 (m, 3H), 7.30 (dd, J = 9.0, 2.6 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H). Anal. ($C_{22}H_{16}N_2O_3$) C, H, N.

Procedure 6. 9-Hydroxy-6-methyl-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (10). Compound **132** (180 mg, 0.50 mmol) was heated in a melt with pyridine hydrochloride (10 g) at 200 °C under nitrogen. After 15 min the reaction mixture was cooled and diluted with water to precipitate the product, which was collected by filtration and washed with water before being dried in vacuo. Chromatography on silica, eluting with ethyl acetate/dichloromethane (1:3), followed by trituration from dichloromethane/hexane, gave **10** (155 mg, 90%) as an orange powder: mp 297−300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.05 (br s, 1H), 9.34 (s, 1H), 8.39 (d, J = 2.5 Hz, 1H), 7.76 (s, 1H), 7.65 (m, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.46 (m, 3H), 7.13 (dd, J = 8.8, 2.5 Hz, 1H), 3.93 (s, 3H). Anal. ($C_{21}H_{14}N_2O_3 \cdot H_2O$) C, H, N.

2,6-Dimethyl-9-methoxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (133). To a stirred solution of 9-hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione[11] (**3**) (0.15 g, 0.46 mmol) in THF/DMF (4:1, 25 mL) under nitrogen was added sodium hydride (110 mg of a 50% dispersion in oil, 2.3 mmol). After 20 min, excess methyl iodide (1.0 mL) was added and the mixture was stirred for a further 30 min before being diluted with water and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Chromatography on silica, eluting with ethyl acetate/hexane (1:1), followed by trituration from methanol, gave **133** (141 mg, 83%) as a yellow powder: mp 237−238 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.49 (d, J = 2.6 Hz, 1H), 7.76 (s, 1H), 7.68−7.61 (m, 3H), 7.51−7.44 (m, 3H), 7.27 (dd, J = 8.9, 2.6 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.05 (s, 3H). Anal. ($C_{23}H_{18}N_2O_3$) C, H, N.

2,6-Dimethyl-9-hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (20). To a stirred solution of **133** (85 mg, 0.21 mmol) in CH_2Cl_2 (20 mL) under nitrogen was added boron tribromide (2.1 mL of a 1 M solution in CH_2Cl_2, 2.1 mmol). After 2 h, the reaction mixture was diluted with water and extracted with ethyl acetate (3×). The combined organic extracts were washed with saturated sodium bicarbonate and then brine before being dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography on silica, eluting with ethyl acetate/hexane (3:2), followed by trituration from methanol, gave **20** (56 mg, 69%) as an orange powder: mp 278−281 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.35 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.74 (s, 1H), 7.65 (m, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.50−7.43 (m, 3H), 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 3.91 (s, 3H), 3.06 (s, 3H). Anal. ($C_{22}H_{16}N_2O_3$) C, H, N.

9-Hydroxy-4-phenyl-1*H*-furo[3,4-*c*]carbazole-1,3-(6*H*)-dione (21). 9-Methoxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione[11] (677 mg, 1.98 mmol) was heated in a melt with pyridine hydrochloride (50 g) at 200 °C under nitrogen. After 25 min the reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (3×). The combined organic extracts were washed with saturated sodium bicarbonate and then brine before being dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography on silica, eluting with ethyl acetate/dichloromethane (1:9 to 1:3), gave at highest R_f **21** (108 mg, 17%) as an orange powder: mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.13 (br s, 1H), 9.43 (br s, 1H), 8.20 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H), 7.67 (m, 2H), 7.54−7.46 (m, 4H), 7.14 (dd, J = 8.7, 2.4 Hz, 1H). EIMS found 329.0691; $C_{20}H_{11}NO_4$ requires 329.0688. Further elution gave at lowest R_f 9-hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione[11] (**3**) (510 mg, 78%). ^{1}H NMR data are identical to those for an authentic sample.

2-Amino-9-hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (22). To a solution of **3**[11] (80 mg, 0.24 mmol) in ethanol (10 mL) was added hydrazine hydrate (0.12 mL, 2.4 mmol). The reaction mixture was heated at reflux for 30 min, and then concentrated sulfuric acid (4 drops) was added. Reflux was continued overnight, and then the mixture was poured onto ice. The orange precipitate was collected by filtration to give **22** (67 mg, 80%): mp 280−286 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.75 (br s, 1H), 9.28 (br s, 1H), 8.37 (d, J = 2.4 Hz, 1H), 7.61−7.59 (m, 2H), 7.56 (s, 1H), 7.50−7.43 (m, 4H), 7.07 (dd, J = 8.7, 2.4 Hz, 1H), 4.85 (s, 2H). EIMS found 343.0961; $C_{20}H_{13}N_3O_3$ requires 343.0957.

2-[2-(2-Chlorophenyl)ethenyl]-5-methoxy-1*H*-indole (113). Lithium diisopropylamide (34.4 mL of a 1.5 N solution, 0.052 mol) was added dropwise under nitrogen to a suspension of (2-chlorobenzyl)(triphenyl)phosphonium chloride (20.17 g, 0.048 mol) in dry THF (200 mL), and the solution was stirred at room temperature for 15 min. A solution of 5-methoxy-1*H*-indole-2-carbaldehyde (**106**) (6.99 g, 0.040 mol) in THF (30 mL) was added, and stirring was continued at room temperature for 15 min. Then the reaction mixture was heated at reflux for 6 h. The cooled solution was diluted with water and extracted with EtOAc, and the organic phase was dried. The drying agent was removed, and the solution was concentrated to dryness to give an oil, which was adsorbed onto silica and chromatographed on silica. Elution with ethyl acetate/petroleum ether (1:1) gave **113** (**II**, 5-OMe, Ar = 2-chlorophenyl) as a mixture of *E*/*Z* isomers (9.76 g, 87%). Crystallization of a small sample from methanol afforded pure *E*-isomer: mp 135−137 °C; ^{1}H NMR ($CDCl_3$) δ 11.39 (s, 1H), 7.86 (dd, J = 7.8, 1.5 Hz, 1H), 7.49 (dd, J = 8.0, 1.2 Hz, 1H), 7.43 (d, J = 16.4 Hz, 1H), 7.37 (m, 1H), 7.31−7.23 (m, 3H), 7.01 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.7, 2.4 Hz, 1H), 6.56 (s, 1H), 3.75 (s, 3H). Anal. ($C_{17}H_{14}ClNO$) C, H, N.

4-(2-Chlorophenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (24). A solution of **113** (1.5 g, 5.29 mmol), maleimide (0.61 g, 6.34 mmol), and $SnCl_2$ (0.20 g, 1.05 mmol) in toluene (25 mL) was refluxed for 6 h. After dilution with ethyl acetate, the solution was washed with water and the organic phase was dried. The drying agent was removed, and the solution was concentrated to dryness to give 4-(2-chlorophenyl)-9-methoxy-4,5,6,10c-tetrahydropyrrolo[3,4-*c*]carbazole-1,3(2*H*,3a*H*)-dione (**134**) (**IV**, 9-OMe, R = H, Ar = 2-chlorophenyl) (1.98 g, 98%) as a yellow solid (a mixture of diastereomers), which was used without further purification.

Procedure 7. Manganese dioxide (12.0 g) was added to a solution of **134** (2.1 g, 5.51 mmol) in dioxane (100 mL), and the mixture was refluxed with stirring for 16 h. The mixture was filtered hot through a plug of Celite, washing through with more dioxane and then 10% methanol/dioxane. The combined filtrate and washings were concentrated to dryness, and the residue was adsorbed onto silica and chromatographed. Elution with ethyl acetate/petroleum ether (3:7) gave **24** (1.66 g, 79%), which crystallized from THF/petroleum ether as a yellow powder: mp 170−175 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.96 (br s, 1H), 11.08 (br s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.60−7.55 (m, 3H), 7.51−7.42 (m, 3H), 7.24 (dd, J = 8.9, 2.6 Hz, 1H), 3.89 (s, 3H). Anal. ($C_{21}H_{13}ClN_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

4-(2-Chlorophenyl)-9-methoxy-1*H*-[1]benzofuro[3,2-*e*]isoindole-1,3(2*H*)-dione (136). Reaction of 5-methoxy-1-benzofuran-2-carbaldehyde[24] with (2-chlorobenzyl)(triphenyl)phosphonium bromide using procedure 2 gave 5-methoxy-2-[(*E,Z*)-2-(2-chlorophenyl)-ethenyl]-1-benzofuran (**135**) as a 2:1 mixture of *E*/*Z* isomers (24%), which was used without further purification.

Reaction of **135** with maleimide using procedure 3 and aromatization with MnO_2 using procedure 7 gave **136** (49%): mp 246−248 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.46 (br s, 1H), 8.22 (d, J = 2.7 Hz, 1H), 7.99 (s, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.61−7.58 (m, 1H), 7.53−7.44 (m, 3H), 7.33 (dd, J = 9.0, 2.7 Hz, 1H), 3.92 (s, 3H). Anal. ($C_{21}H_{12}ClNO_4$) C, H, N.

4-(2-Chlorophenyl)-9-hydroxy-1*H*-[1]benzofuro[3,2-*e*]isoindole-1,3(2*H*)-dione (26). Demethylation of **136** with BBr_3 using procedure 5 gave **26** (89%): mp 140−145 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.39 (br s, 1H), 9.78 (s, 1H), 8.12 (d, J = 2.6 Hz, 1H), 7.93 (s, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.60−7.58 (m, 1H), 7.52−7.43 (m, 3H), 7.13 (dd, J = 8.9, 2.6 Hz, 1H). EIMS found M^+, 363.0294, 365.0269; $C_{20}H_{10}ClNO_4$ requires 363.0298, 365.0289.

2-[(*E*)-2-(2-Bromophenyl)ethenyl]-5-methoxy-1*H*-indole (137). Reaction of **106** and (2-bromobenzyl)(triphenyl)phosphonium bromide using procedure 2 gave **137** (**II**, 5-OMe, Ar = 2-bromophenyl) (88%): mp (DCM/hexane) 120−123 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (br s, 1H), 7.66 (dd, J = 7.9, 1.5 Hz, 1H), 7.59 (dd, J = 8.1, 1.0 Hz, 1H), 7.32 (br t, J = 7.1 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 16.4 Hz, 1H), 7.12 (td, J = 7.6, 1.5 Hz, 1H), 7.05 (d, J = 16.4 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.8, 2.4 Hz, 1H), 6.59 (d, J = 1.7 Hz, 1H), 3.86 (s, 3H). Anal. ($C_{17}H_{14}BrNO$) C, H, N.

4-(2-Bromophenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (138). Maleimide (1.48 g, 15.2 mmol) and **137** (1.00 g, 3.05 mmol) were reacted in dry toluene (10 mL) in a sealed vial at reflux for 24 h, and the product was treated with DDQ (3.49 g, 15.4 mmol) in toluene (30 mL) and dioxane (40 mL), stirring under reflux for 24 h. The resulting mixture was partitioned between saturated aqueous $NaHCO_3$ (250 mL) and 15% MeOH/DCM. The organic extracts were washed with aqueous $NaHCO_3$ solution and water, the aqueous layers were back-extracted with 15% MeOH/DCM, and the combined organic extracts were concentrated to dryness. The residue was chromatographed on silica gel, eluting with 0−0.75% MeOH/DCM and then with 0.75% MeOH/DCM, to give **138** (**V**, 9-OMe, R = H, Ar = 2-bromophenyl) (1.23 g, 96%): mp (MeOH/DCM/hexane) 273−275 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.96 (br s, 1H), 11.08 (br s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.9 Hz, 1H), 7.55 (s, 1H), 7.48 (m, 2H), 7.39 (m, 1H), 7.25 (dd, J = 8.9, 2.7 Hz, 1H), 3.89 (s, 3H). Anal. ($C_{21}H_{13}BrN_2O_3$) C, H, N.

4-(2-Bromophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (28). Demethylation of **138** with BBr_3 for 4 h using procedure 5 gave **28** (89%): mp (MeOH/DCM/hexane) 244−246 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.83 (br s, 1H), 11.01 (br s, 1H), 9.29 (br s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.73 (br d, J = 7.9 Hz, 1H), 7.47 (m, 4H), 7.38 (m, 1H), 7.08 (dd, J = 8.7, 2.5 Hz, 1H). Anal. ($C_{20}H_{11}BrN_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

4-(2-Aminophenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (139). A solution of **149** (see later for preparation) (71 mg, 0.183 mmol) in 2:1 THF/MeOH (45 mL) containing wet 10% Pd−C (71 mg) was hydrogenated at 60 psi for 7 h. The solution was filtered through Celite and washed thoroughly with MeOH and THF. Then the filtrate was concentrated to dryness to give **139** (**V**, 9-OMe, R = H, Ar = 2-aminophenyl) (67 mg, 97%) as a yellow solid: mp (MeOH/DCM/hexane) >320 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.80 (br s, 1H), 10.94 (br s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.51 (s, 1H), 7.21 (dd, J = 8.8, 2.6 Hz, 1H), 7.08 (td, J = 7.7, 1.5 Hz, 1H), 7.01 (dd, J = 7.6, 1.5 Hz, 1H), 6.73 (dd, J = 8.1, 0.6 Hz, 1H), 6.61 (td, J = 7.4, 0.9 Hz, 1H), 4.70 (s, 2H), 3.89 (s, 3H). Anal. ($C_{21}H_{15}N_3O_3 \cdot H_2O$) C, H, N.

4-(2-Iodophenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (140). A solution of **139** (46 mg, 0.129 mmol) in 90% H_2SO_4 (2.5 mL) was cooled to −5 °C, diluted with ice−water (2.5 mL), then allowed to warm to 7 °C. The resulting suspension was treated dropwise with a solution of $NaNO_2$ (13.6 mg, 0.197 mmol) in cold water (2 × 0.5 mL) and stirred at 7 °C for 8 min. A solution of urea (5 mg, 0.083 mmol) in cold water (2 × 0.4 mL) was added, and the mixture was stirred at 7 °C for 4 min. Finally, a suspension of KI (140 mg, 0.843 mmol) and CuI (140 mg, 0.735 mmol) in cold water (2 × 1 mL) was added. Then the cooling bath was removed, and the mixture was stirred for 10 min and then at 60−65 °C for 2 h. An aqueous solution of sodium metabisulfite (100 mL of 0.5%) was added, and then the mixture was extracted with 20% THF/EtOAc (5 × 100 mL). The extracts were washed with water (200 mL), the water was extracted with EtOAc, and the combined organic extracts were concentrated to dryness. The residue was chromatographed twice on silica gel, eluting with 0−0.5% MeOH/DCM and 0.5% MeOH/DCM, and then on the second column with 1% EtOH/$CHCl_3$ to give **140** (**V**, 9-OMe, R = H, Ar = 2-iodophenyl) (18 mg, 30%): mp (MeOH/THF/DCM/hexane) 311−315 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.95 (br s, 1H), 11.07 (br s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.97 (dd, J = 7.7, 0.9 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.50 (td, J = 7.6, 0.9 Hz, 1H), 7.48 (s, 1H), 7.44 (dd, J = 7.6, 1.8 Hz, 1H), 7.25 (dd, J = 8.9, 2.7 Hz, 1H), 7.19 (td, J = 7.6, 1.8 Hz, 1H), 3.89 (s, 3H). Anal. ($C_{21}H_{13}IN_2O_3$) C, H, N.

4-(2-Iodophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (29). Demethylation of **140** with BBr_3 using procedure 5 gave **29** (88%): mp (MeOH/DCM/hexane) 217−223 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.82 (br s, 1H), 11.01 (br s, 1H), 9.28 (br s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.96 (br d, J = 7.8 Hz, 1H), 7.49 (br t, J = 7.7 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.42 (s, 1H), 7.42 (dd, J = 7.4, 1.7 Hz, 1H), 7.19 (td, J = 7.6, 1.7 Hz, 1H), 7.08 (dd, J = 8.7, 2.5 Hz, 1H). Anal. ($C_{20}H_{11}IN_2O_3$) C, H, N.

(2-Cyanobenzyl)(triphenyl)phosphonium Bromide (141). Bromination of *o*-tolunitrile with NBS/AIBN, followed by reaction of the crude bromide with triphenylphosphine (1.2 equiv.), using procedure 1, except that the reaction time for the bromination was 2 h, gave **141** (70%) as a light-brown powder: mp (CH_2Cl_2/benzene) 237−241 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (dd, J = 7.8, 2.3 Hz, 1H), 7.85−7.63 (m, 15H), 7.52 (br t, J = 7.7 Hz, 1H), 7.44 (br d, J = 7.5 Hz, 1H), 7.38 (tdd, J = 7.6, 2.1, 1.0 Hz, 1H), 5.86 (d, J = 14.7 Hz, 2H). Anal. ($C_{26}H_{21}BrNP$) C, H, N.

2-[(*E*)-2-(5-Methoxy-1*H*-indol-2-yl)ethenyl]benzonitrile (142). 5-Methoxy-1*H*-indole-2-carbaldehyde (**106**) was reacted with **141** as described in procedure 2, except that the LDA and aldehyde were (sequentially) added at 0 °C and the ratio LDA/aldehyde was 1.55:1, to give (after crystallization from CH_2Cl_2/hexane) the diene **142** (**II**, 5-OMe, Ar = 2-cyanophenyl) as a yellow solid (the pure *E* isomer) (60%): mp 192−196 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 8.1, 0.9 Hz, 1H), 7.58 (td, J = 7.9, 1.3 Hz, 1H), 7.32 (td, J = 8.0, 0.9 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 16.9 Hz, 1H), 7.18 (d, J = 16.4 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.9, 2.4 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H). Anal. ($C_{18}H_{14}N_2O$) C, H, N.

2-(9-Methoxy-1,3-dioxo-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazol-4-yl)benzonitrile (143). The *E* diene **142** was subjected to successive reactions with maleimide and then DDQ as described in procedures 3 and 4 except that the poorly soluble final product was obtained by removal of the reaction solvents, washing of the solid residue thoroughly with aqueous $NaHCO_3$ solution and water, and then trituration in 15% MeOH/CH_2Cl_2 and crystallization of the liquors from THF/CH_2Cl_2/hexane to give **143** (**V**, 9-OMe, R = H, Ar = 2-cyanophenyl) (96%) as a yellow solid: mp 348−350 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.06 (br s, 1H), 11.19 (br s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 7.96 (dd, J = 7.7, 1.0 Hz, 1H), 7.82 (td, J = 7.7, 1.4 Hz, 1H), 7.71 (br d, J = 7.4 Hz, 1H), 7.71 (s, 1H), 7.66 (td, J = 7.6, 1.1 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.27 (dd, J = 8.8, 2.6 Hz, 1H), 3.90 (s, 3H). EIMS found M^+, 367.0956; $C_{22}H_{13}N_3O_3$ requires 367.0957.

2-(9-Hydroxy-1,3-dioxo-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazol-4-yl)benzonitrile (34). The methyl ether **143** was demethylated with BBr_3 using procedure 5, except that the reaction time was 5 h with 5 equiv of BBr_3 and then a further 4 h with an extra

5 equiv of BBr_3, to give (after crystallization from THF/CH_2Cl_2/hexane) the phenol **34** (83%) as a yellow solid: mp 199−204 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.93 (br s, 1H), 11.13 (br s, 1H), 9.31 (br s, 1H), 8.34 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 7.6, 0.9 Hz, 1H), 7.82 (td, J = 7.7, 1.4 Hz, 1H), 7.70 (br d, J = 7.5 Hz, 1H), 7.65 (s, 1H), 7.65 (td, J = 7.7, 1.0 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.10 (dd, J = 8.7, 2.5 Hz, 1H). Anal. ($C_{21}H_{11}N_3O_3 \cdot {}^1/_4H_2O$) C, H, N.

2-(9-Methoxy-1,3-dioxo-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazol-4-yl)benzamide (145). Hydrogen peroxide (0.5 mL of a 35% aqueous solution, 5.8 mmol) was added dropwise to a stirred mixture of carbazole methyl ether **143** (61 mg, 0.166 mmol) and potassium carbonate (229 mg, 1.66 mmol) in DMSO (3 mL), and then the mixture was stirred at room temperature for 26 h. Further hydrogen peroxide (0.5 mL) in DMSO (3 mL) was added, and the mixture was stirred at 50 °C for 4 days. The cooled solution was diluted with water (100 mL) and extracted with EtOAc (4 × 100 mL). The aqueous portion was then acidified (to pH 2) with concentrated HCl and extracted with EtOAc (4 × 100 mL). These extracts were washed with water (100 mL), back-extracted with EtOAc (100 mL), and evaporated to dryness to give crude 2-(9-methoxy-1,3-dioxo-3,6-dihydro-1*H*-furo[3,4-*c*]carbazol-4-yl)benzamide **(144)** (75 mg) as a solid, which was used directly: ^{1}H NMR [$(CD_3)_2SO$] δ 12.26 (br s, 1 H), 8.27 (d, J = 2.5 Hz, 1 H), 7.74 (s, 1 H), 7.71−7.48 (m, 6 H), 7.30 (dd, J = 8.9, 2.6 Hz, 1 H), 7.21 (br s, 1 H), 3.91 (s, 3 H). FABMS found $[M]^+$, 386.0905; $C_{22}H_{14}N_2O_5$ requires 386.0903.

A mixture of crude anhydride **144** (73 mg) and ammonium acetate (10 g) was stirred at 141 °C for 7 h. The cooled solution was added to a mixture of ice and aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (5 × 100 mL). The combined extracts were washed with water (200 mL) and evaporated to dryness, and then the residue was recrystallized to give **145** (**V**, 9-OMe, R = H, Ar = 2-benzamide) (55 mg, 76% for 2 steps) as a yellow solid: mp (MeOH/THF/EtOAc/pentane) 345−348 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.87 (br s, 1 H), 10.97 (br s, 1 H), 8.46 (d, J = 2.6 Hz, 1 H), 7.62 (m, 1 H), 7.56−7.38 (m, 6 H), 7.22 (dd, J = 8.8, 2.5 Hz, 1 H), 7.14 (br s, 1 H), 3.89 (s, 3 H). Anal. ($C_{22}H_{15}N_3O_4$) C, H, N.

2-(9-Hydroxy-1,3-dioxo-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazol-4-yl)benzamide (36). Boron tribromide (2.0 mL of a 1.0 M solution in CH_2Cl_2, 2.0 mmol) was added to a stirred solution of carbazole methyl ether **145** (44.6 mg, 0.103 mmol) in dry CH_2Cl_2 (3 mL) under N_2, and then the mixture was stirred at room temperature for 5 h. The resulting solution was added to a mixture of ice and aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (5 × 100 mL). The combined extracts were washed with water (200 mL) and evaporated to dryness, and then the residue was chromatographed on silica gel. Elution with 50−80% EtOAc/light petroleum gave foreruns. Then further elution with 80% EtOAc/light petroleum and EtOAc gave **36** (34 mg, 89%) as an orange solid following recrystallization: mp (THF/hexane) 330−334 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.73 (br s, 1 H), 10.91 (br s, 1 H), 9.23 (br s, 1 H), 8.31 (d, J = 2.4 Hz, 1 H), 7.61 (m, 1 H), 7.54−7.37 (m, 6 H), 7.13 (br s, 1 H), 7.05 (dd, J = 8.7, 2.5 Hz, 1 H). Anal. ($C_{21}H_{13}N_3O_4$) C, H, N.

4-[1,1′-Biphenyl]-2-yl-9-methoxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (146). A mixture of bromide **138** (85.5 mg, 0.203 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium-(II)·DCM (85 mg, 0.104 mmol), and tetraphenyltin (0.451, 1.06 mmol) in dry DMF (2.5 mL) was stirred in a sealed vial at 130 °C for 4 days. The mixture was then partitioned between aqueous $NaHCO_3$ (100 mL) and 2:1 CH_2Cl_2/EtOAc (5 × 80 mL), and the combined organic extracts were concentrated to dryness. The residue was chromatographed several times on silica gel, eluting with DCM, to give the crude product. This was further purified by preparative reversed phase C-18 HPLC, using a gradient of 65−99% MeCN/aqueous HCO_2NH_4 buffer, pH 3.45, to give **146** (**V**, 9-OMe, R = H, Ar = 2-biphenyl) (21%): mp (MeOH/DCM/hexane) 220−223 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.76 (br s, 1H), 10.87 (br s, 1H), 8.39 (d, J = 2.6 Hz, 1H), 7.50 (m, 5H), 7.38 (s, 1H), 7.20 (dd, J = 8.9, 2.6 Hz, 1H), 7.10 (m, 5H), 3.86 (s, 3H). Anal. ($C_{27}H_{18}N_2O_3$) C, H, N.

4-[1,1′-Biphenyl]-2-yl-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (37). Demethylation of **146** with BBr_3 for 4 h using procedure 5 gave **37** (98%): mp (MeOH/DCM/hexane) 198−203 °C (dec). ^{1}H NMR [$(CD_3)_2SO$] δ 11.61 (br s, 1H), 10.82 (br s, 1H), 9.22 (br s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 7.52 (m, 1H), 7.45 (m, 3H), 7.37 (d, J = 8.7 Hz, 1H), 7.31 (s, 1H), 7.11 (m, 5H), 7.03 (dd, J = 8.7, 2.5 Hz, 1H). Anal. ($C_{26}H_{16}N_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

4-(2-Hydroxyphenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (147). Diazotization of **139** as described above for the preparation of **140** and elution of the first chromatography column with 1% MeOH/DCM gave **147** (**V**, 9-OMe, R = H, Ar = 2-hydroxyphenyl) (24%): mp (THF/DCM/pentane) 264−267 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.82 (br s, 1H), 10.95 (br s, 1H), 9.41 (br s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 7.56 (s, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.25 (dd, J = 7.4, 1.6 Hz, 1H), 7.23 (td, J = 7.9, 1.7 Hz, 1H), 7.22 (dd, J = 8.7, 2.6 Hz, 1H), 6.91 (br d, J = 7.5 Hz, 1H), 6.87 (td, J = 7.4, 0.9 Hz, 1H), 3.89 (s, 3H). Anal. ($C_{21}H_{14}N_2O_4$) C, H, N.

9-Hydroxy-4-(2-hydroxyphenyl)pyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (38). Demethylation of **147** with BBr_3 for 4 h using procedure 5 gave **38** (73%): mp (MeOH/THF/CH_2Cl_2/hexane) 291−296 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.67 (br s, 1H), 10.88 (br s, 1H), 9.37 (br s, 1H), 9.22 (br s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.51 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.24 (dd, J = 7.5, 1.5 Hz, 1H), 7.22 (td, J = 7.7, 1.8 Hz, 1H), 7.05 (dd, J = 8.7, 2.5 Hz, 1H), 6.91 (br d, J = 8.0 Hz, 1H), 6.86 (td, J = 7.4, 0.9 Hz, 1H). Anal. ($C_{20}H_{12}N_2O_4 \cdot H_2O$) C, H, N.

5-Methoxy-2-[(*E*)-2-(2-nitrophenyl)ethenyl]-1*H*-indole (148). Reaction of **106** and (2-nitrobenzyl)(triphenyl)phosphonium chloride using procedure 2 gave **148** (**II**, 5-OMe, Ar = 2-nitrophenyl) (47%): mp (DCM/hexane) 136−138 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (br s, 1H), 7.98 (dd, J = 8.2, 1.2 Hz, 1H), 7.78 (dd, J = 7.9, 1.0 Hz, 1H), 7.61 (td, J = 7.6, 0.9 Hz, 1H), 7.41 (d, J = 16.3 Hz, 1H), 7.39 (td, J = 7.8, 1.3 Hz, 1H), 7.27 (m, 1H), 7.13 (d, J = 16.3 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.8, 2.5 Hz, 1H), 6.62 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H). Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

9-Methoxy-4-(2-nitrophenyl)pyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (149). Reaction of **148** successively with maleimide using procedure 3 and then DDQ using procedure 4 gave **149** (**V**, 9-OMe, R = H, Ar = 2-nitrophenyl) (97%): mp (MeOH/EtOAc/DCM/hexane) 294−298 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.01 (br s, 1H), 11.10 (br s, 1H), 8.44 (d, J = 2.5 Hz, 1H), 8.21 (dd, J = 8.1, 1.0 Hz, 1H), 7.86 (td, J = 7.5, 1.4 Hz, 1H), 7.74 (td, J = 7.8, 1.3 Hz, 1H), 7.67 (s, 1H), 7.65 (dd, J = 7.6, 1.4 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.25 (dd, J = 8.7, 2.6 Hz, 1H), 3.90 (s, 3H). Anal. ($C_{21}H_{13}N_3O_5$) C, H, N.

9-Hydroxy-4-(2-nitrophenyl)pyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (43). Demethylation of **149** using procedure 5 for 5 h with 5 equiv of BBr_3 and then for a further 21 h with an extra 5 equiv of BBr_3 gave **43** (53%): mp (MeOH/DCM/hexane) 322−330 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.88 (br s, 1H), 11.05 (br s, 1H), 9.29 (br s, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 8.2, 1.1 Hz, 1H), 7.85 (td, J = 7.5, 1.2 Hz, 1H), 7.73 (td, J = 7.9, 1.4 Hz, 1H), 7.63 (dd, J = 7.6, 1.4 Hz, 1H), 7.61 (s, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.09 (dd, J = 8.7, 2.5 Hz, 1H). Anal. ($C_{20}H_{11}N_3O_5 \cdot {}^1/_2$-MeOH) C, H, N.

4-(2-Aminophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (44). A solution of **43** (81 mg, 0.217 mmol) in 2:1 THF/MeOH (60 mL) containing wet 10% Pd−C (81 mg) was hydrogenated at 60 psi for 12 h. The solution was filtered through Celite, the Celite and catalyst were washed thoroughly with MeOH and THF, and the combined filtrates were evaporated to give **44** (60 mg, 81%): mp (MeOH/DCM/hexane) >330 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.67 (br s, 1H), 10.88 (br s, 1H), 9.21 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.46 (s, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.08 (td, J = 7.9, 1.5 Hz, 1H), 7.05 (dd, J = 8.7, 2.4 Hz, 1H), 7.00 (dd, J = 7.6, 1.4 Hz, 1H), 6.72 (br d, J = 8.1 Hz, 1H), 6.60 (td, J = 7.4, 0.9 Hz, 1H), 4.69 (s, 2H). Anal. ($C_{20}H_{13}N_3O_3 \cdot H_2O$) C, H, N.

2-[(*E*)-2-(2-Chloro-5-methoxyphenyl)ethenyl]-5-methoxy-1*H*-indole (150). Reaction of **106** and (2-chloro-5-methoxybenzyl)-(triphenyl)phosphonium bromide[26] using procedure 2 gave **150** (**II**, 5-OMe, Ar = 2-chloro-5-methoxyphenyl) (85%): mp (DCM/hexane) 119−121 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (br s, 1H), 7.29 (d, J = 8.9 Hz, 1H), 7.26 (br d, J = 8.7 Hz, 1H), 7.22 (d, J = 16.5 Hz, 1H), 7.18 (d, J = 3.0 Hz, 1H), 7.06 (d, J = 16.7 Hz, 1H), 7.04 (br s, 1 H), 6.88 (dd, J = 8.7, 2.5 Hz, 1H), 6.77 (dd, J = 8.8, 3.0 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H). Anal. ($C_{18}H_{16}ClNO_2$) C, H, N.

4-(2-Chloro-5-methoxyphenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (151). Successive reaction of **150** with maleimide using procedure 3 and then with DDQ using procedure 4 gave **151** (**V**, 9-OMe, R = H, Ar = 2-chloro-5-methoxyphenyl) (84%): mp (MeOH/DCM/hexane) 284−286 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 11.96 (br s, 1H), 11.08 (br s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.58 (s, 1H), 7.57 (m, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.25 (dd, J = 8.8, 2.6 Hz, 1H), 7.07 (d, J = 2.9 Hz, 1H), 7.04 (dd, J = 8.7, 3.1 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H). Anal. ($C_{22}H_{15}ClN_2O_4 \cdot H_2O$) C, H, N.

4-(2-Chloro-5-hydroxyphenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (76). Bis-demethylation of **151** for 6.5 h with 10 equiv of BBr_3 using procedure 5 gave **76** (90%): mp (MeOH/DCM/hexane) 335−340 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 11.80 (br s, 1H), 11.00 (br s, 1H), 9.78 (br s, 1H), 9.27 (br s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.49 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.07 (dd, J = 8.7, 2.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.9 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H). Anal. ($C_{20}H_{11}ClN_2O_4 \cdot {}^1/_2H_2O \cdot {}^1/_4$hexane) C, H, N.

(2-Chloro-5-nitrobenzyl)(triphenyl)phosphonium Bromide (152). Bromination of (2-chloro-5-nitrophenyl)methanol with 30% HBr in acetic acid, followed by reaction of the crude bromide with triphenylphosphine using procedure 1, gave **152** (63%): mp (CH_2Cl_2/benzene) 239−243 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (br s, 1 H), 8.07 (br d, J = 8.7 Hz, 1 H), 7.87−7.65 (m, 15 H), 7.41 (d, J = 8.9 Hz, 1 H), 5.80 (d, J = 14.8 Hz, 2 H). Anal. ($C_{25}H_{20}BrClNO_2P$) C, H, N.

2-[(*E*)-2-(2-Chloro-5-nitrophenyl)ethenyl]-5-methoxy-1*H*-indole (153). Reaction of **106** and **152** using procedure 2 gave **153** (**II**, 5-OMe, Ar = 2-chloro-5-nitrophenyl) (57%): mp (DCM/pentane) 191−193 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 2.6 Hz, 1H), 8.25 (br s, 1H), 8.02 (dd, J = 8.8, 2.6 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.26 (d, J = 16.4 Hz, 1H), 7.20 (d, J = 16.5 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 6.70 (br s, 1H), 3.86 (s, 3H). Anal. ($C_{17}H_{13}ClN_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

4-(2-Chloro-5-nitrophenyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (154). Successive reaction of **153** with maleimide using procedure 3 and then DDQ using procedure 4 gave **154** (**V**, 9-OMe, R = H, Ar = 2-chloro-5-nitrophenyl) (95%): mp THF/DCM/pentane) 285−287 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 12.06 (br s, 1H), 11.16 (br s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.36 (d, J = 2.8 Hz, 1H), 8.33 (dd, J = 8.7, 2.7 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.71 (s, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.27 (dd, J = 8.9, 2.6 Hz, 1H), 3.90 (s, 3H). Anal. ($C_{21}H_{12}ClN_3O_5 \cdot {}^1/_4CH_2Cl_2$) C, H, N.

4-(2-Chloro-5-nitrophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (**155**). Demethylation of **154** using procedure 5 for 6 h with 10 equiv of BBr_3 and then for a further 4 h with an extra 10 equiv of BBr_3 gave **155** (**VI**, 9-OH, R = H, Ar = 2-chloro-5-nitrophenyl) (88%): mp (THF/CH_2Cl_2/pentane) 268 °C (dec); ^{1}H NMR [$(CD_3)_2$SO] δ 11.94 (br s, 1H), 11.11 (br s, 1H), 9.31 (br s, 1H), 8.35 (d, J = 2.6 Hz, 1H), 8.32 (dd, J = 8.6, 2.9 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.10 (dd, J = 8.7, 2.5 Hz, 1H). Anal. ($C_{20}H_{10}ClN_3O_5 \cdot {}^1/_4H_2O$) C, H, N.

4-(5-Amino-2-chlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (77). A mixture of **155** (70 mg, 0.172 mmol) and freshly prepared (wet) nickel boride (266 mg) in MeOH (5.6 mL) and 1 M HCl (1.4 mL) was stirred at reflux for 3 h. Concentrated aqueous ammonia and aqueous $NaHCO_3$ (100 mL) were added, and the mixture extracted with EtOAc (5 × 70 mL). The extracts were washed with water, concentrated, and chromatographed on silica gel. Elution with 0−2% MeOH/CH_2Cl_2 and then 3% MeOH/CH_2Cl_2 gave **77** (97%): mp (THF/DCM/pentane) 301−306 °C (dec); ^{1}H NMR [$(CD_3)_2$SO] δ 11.78 (br s, 1H), 10.97 (br s, 1H), 9.26 (br s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.45 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 8.7, 2.5 Hz, 1H), 6.62 (dd, J = 8.2, 2.8 Hz, 1H), 6.60 (d, J = 2.3 Hz, 1H), 5.29 (s, 2H). Anal. ($C_{20}H_{12}ClN_3O_3 \cdot {}^1/_4H_2O$) C, H, N.

Procedures of Scheme 2. Benzyl (2*E*)-3-(5-Methoxy-1*H*-indol-2-yl)-2-propenoate (107). Benzyl (triphenylphosphoranylidene)-acetate (49.2 g, 0.120 mol) was added to a stirred solution of 5-methoxy-1*H*-indole-2-carbaldehyde (**106**) (20.0 g, 0.114 mol) in DCM (500 mL), and the solution was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was slurried with MeOH (200 mL), filtered, and washed with cold MeOH to give **107** (30.46 g, 87%): mp 155−157 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1H), 7.69 (d, J = 16.1 Hz, 1H), 7.43−7.32 (m, 5H), 7.23 (d, J = 9.1 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 6.92 (dd, J = 9.1, 2.3 Hz, 1H), 6.74 (d, J = 1.8 Hz, 1H), 6.24 (d, J = 16.1 Hz, 1H), 5.26 (s, 2H), 3.84 (s, 3H). Anal. ($C_{19}H_{17}NO_3$) C, H, N.

Procedure 8. Benzyl 9-Methoxy-1,3-dioxo-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazole-4-carboxylate (109). Maleimide (4.82 g, 0.050 mol) was added to a solution of **107** (12.71 g, 0.041 mol) in THF (150 mL), and the mixture was stirred until it was homogeneous. The THF was evaporated, and the residue was dried under high vacuum for 30 min and then stirred at 175 °C for 3 h. The solid melt was cooled and stirred vigorously with EtOAc (100 mL) overnight. The precipitate was filtered and washed with Et_2O to give benzyl 9-methoxy-1,3-dioxo-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,4-*c*]carbazole-4-carboxylate (**108**) (13.76 g, 83%), which was used directly: mp 179−181 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 10.98 (br s, 1H), 10.87 (s, 1H), 7.45−7.32 (m, 5H), 7.20 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.69 (dd, J = 8.7, 2.4 Hz, 1H), 5.21 (s, 1H), 4.22 (br d, J = 7.8 Hz, 1H), 4.14 (dd, J = 7.8, 4.2 Hz, 1H), 3.75 (s, 3H), 3.19−3.13 (m, 1H), 3.00 (dd, J = 16.5, 4.8 Hz, 1H), 2.79−2.70 (m, 1H).

Activated MnO_2 (69 g) was added to a solution of **108** (13.76 g, 0.034 mol) in dioxane (300 mL), and the mixture was refluxed with vigorous stirring for 2 h. The mixture was filtered while hot through a plug of Celite, which was washed exhaustively with a MeOH/*p*-dioxane (1:1) mixture until the washings were colorless. The combined washings and filtrate were concentrated to dryness, and the residue was triturated several times with Et_2O to give **109** (12.47 g, 91%): mp 245 °C. A sample was crystallized from EtOAc: mp 289−292 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 12.11 (br s, 1H), 11.27 (br s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 7.98 (s, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.55−7.51 (m, 2H), 7.44−7.34 (m, 3H), 7.27 (dd, J = 8.9, 2.6 Hz, 1H), 5.41 (s, 2H), 3.88 (s, 3H). Anal. ($C_{23}H_{16}N_2O_5$) C, H, N.

9-Methoxy-1,3-dioxo-1,2,3,6-tetrahydropyrrolo[3,4-*c*]carbazole-4-carboxylic Acid (110). A solution of **109** (2.00 g) in DMF/MeOH (4:1) (50 mL) containing 5% Pd−C (0.50 g) was hydrogenated at 60 psi for 2 h (Parr apparatus). The solution was filtered through a plug of Celite, which was washed six times with neat DMF followed by MeOH (several cycles). The combined filtrate and washings were concentrated to dryness, and the residue was slurried with Et_2O and filtered. The products from five identical mixtures were combined to give crude **110** (8.1 g, 84%). A sample was purified by chromatography on silica gel, eluting with EtOAc, followed by trituration with Et_2O: mp >300 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 12.15 (s, 1H), 8.42 (d, J = 2.5 Hz, 1H), 7.97 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 8.8, 2.5 Hz, 1H), 3.82 (s, 3H), 3.40 (br, 2H). Anal. ($C_{16}H_{10}N_2O_5 \cdot H_2O$) C, H, N.

4-Amino-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (111). Diphenylphosphorylazide (1.81 mL, 8.38 mmol) was added to a mixture of **110** (2.55 g, 8.22 mmol) and Et_3N (1.17 mL, 8.38 mmol) in anhydrous *t*-BuOH (300 mL), and the mixture was refluxed under nitrogen for 16 h. The solution was evaporated, and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. Insoluble material was removed by filtration of the two layers through Celite, washing with more EtOAc. The organic phase

was dried and evaporated, and the residue was dissolved in DCM/TFA (1:1) (200 mL) and kept at room temperature for 1 h. The solvents were evaporated, and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The EtOAc solution was dried and evaporated, and the residue was chromatographed on silica gel, eluting with EtOAc/petroleum ether (1:1) followed by EtOAc and then MeOH/EtOAc (1:9), to give **111** (2.16 g, 93%): mp 342−345 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.18 (s, 1H), 10.78 (br s, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.01 (dd, J = 8.7, 2.5 Hz, 1H), 6.83 (s, 1H), 6.28 (br s, 2H), 3.82 (s, 3H). Anal. ($C_{15}H_{11}N_3O_3 \cdot {}^1/_2H_2O$) C, H, N.

4-Iodo-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (112). Concentrated H_2SO_4 (10 mL) was added at room temperature to powdered **111** (0.50 g, 1.78 mmol), and the mixture was stirred for 5 min and then cooled in an ice bath. An ice−water slurry (~40 mL) was added in one portion with vigorous stirring, and the mixture was stirred for a further 15 min. When the internal temperature had reached 3 °C, a solution of $NaNO_2$ (0.18 g, 2.65 mmol) in cold water (1 mL) was added dropwise over 30 s, and the mixture was stirred for an additional 3 min. Powdered urea (74 mg, 1.23 mmol) was added, and the mixture was stirred for another 3 min. Finally a suspension of KI (1.46 g, 8.79 mmol) and CuI (1.46 g, 7.66 mmol) in cold water (10 mL) was added, and the mixture was stirred vigorously for 5 min and then warmed slowly to 70 °C and held at this temperature for 1 h. EtOAc was added, and the two-phase mixture was filtered through a plug of Celite and washed with more EtOAc. The combined organic portions were washed with 0.5 N aqueous Na_2SO_3 and evaporated, and the residue was chromatographed on silica gel. Elution with EtOAc gave **112** (0.32 g, 46%): mp (THF/petroleum ether) 322−325 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.89 (s, 1H), 11.29 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.18 (s, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.24 (dd, J = 8.9, 2.6 Hz, 1H), 3.87 (s, 3H). Anal. ($C_{15}H_9IN_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

9-Hydroxy-4-iodopyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (5). Powdered **112** (0.50 g, 1.27 mmol) was added in one portion to a dry, freshly prepared pyridine hydrochloride melt at 200 °C under a $CaCl_2$ drying tube, and the mixture was stirred at this temperature for 15 min. The mixture was partitioned between EtOAc and water, and the EtOAc extracts were dried and evaporated. The residue was chromatographed on silica gel, eluting with EtOAc, to give **5** (0.43 g, 89%): mp >350 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.76 (br s, 1H), 11.24 (br s, 1H), 9.29 (br s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.13 (s, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.08 (dd, J = 8.7, 2.4 Hz, 1H). Anal. ($C_{14}H_7IN_2O_3$) C, H, N.

Procedure 9. 4-(2-Chlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (23). A mixture of **5** (41.8 mg, 0.110 mmol) and 2-chlorobenzeneboronic acid (52 mg, 0.332 mmol) in *p*-dioxane (3 mL) and 2 N Na_2CO_3 (0.5 mL) was purged with nitrogen. Pd(dppf)Cl_2 (35 mg, 0.011 mmol) was added, and the mixture was refluxed under N_2 for 4 h and then partitioned between EtOAc and water. The organic layer was dried and evaporated, and the residue was chromatographed on silica gel, eluting with EtOAc/petroleum ether (1:4) followed by EtOAc/petroleum ether (2:3), to give **23** (33.1 mg, 83%): mp (EtOAc/petroleum ether) 215−220 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.83 (br s, 1H), 11.01 (br s, 1H), 9.27 (br s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.65−7.40 (m, 5H), 7.08 (dd, J = 8.7, 2.4 Hz, 1H). Anal. ($C_{20}H_{11}ClN_2O_3 \cdot {}^1/_4$EtOAc) C, H, N.

Procedures of Scheme 3. Procedure 10. 1-(5-Methoxy-1*H*-indol-2-yl)ethanone (156). A solution of 5-methoxy-1*H*-indole-2-carbaldehyde (**106**)[20,21] (2.0 g, 11.0 mmol) in THF (30 mL) at 0 °C was treated dropwise with a solution of methylmagnesium bromide (11 mL of a 3 M solution in Et_2O, 34.0 mmol). The solution was allowed to warm to room temperature over 50 min, saturated NH_4Cl was then added, solvent was removed under reduced pressure, and the residue was extracted with EtOAc (2 × 60 mL). The combined extracts were washed, dried, and concentrated, and the product was dissolved in $CHCl_3$ (40 mL) and treated with MnO_2 (15 g, 0.171 mol) at reflux for 40 min. The mixture was filtered through Celite and concentrated to give **156** (**IX**, X = Me) (1.80 g, 83%): mp (DCM) 170−172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.58 (br s, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.23 (s, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 9.0, 2.4 Hz, 1H), 3.77 (s, 3H), 2.52 (s, 3H). Anal. ($C_{11}H_{11}NO_2$) C, H, N.

Procedure 11. 9-Hydroxy-5-methyl-4-phenylpyrrolo[3,4-*c*]-carbazole-1,3(2*H*,6*H*)-dione (11). A suspension of benzyl(triphenyl)phosphonium bromide (3.4 g, 7.9 mmol) in THF (30 mL) was treated with a solution of LDA (4.9 mL of a 1.5 M solution in cyclohexane, 7.4 mmol). The red-orange reaction mixture was stirred for 10 min, and then a solution of **156** (1.0 g, 5.3 mmol) in THF (15 mL) was added. The mixture was heated at reflux overnight. Then water was added and the solvent was removed under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL), and the combined extracts were dried and evaporated. The residue was chromatographed on silica gel, eluting with DCM, to give methyl 2-[(*E,Z*)-1-methyl-2-phenylethenyl]-1*H*-indol-5-yl ether (**157**) (**X**, X = Me, Y = phenyl) (0.26 g, 19%) as a mixture of *E* and *Z* isomers, which was used without further purification.

Reaction of **157** with maleimide at 180 °C for 40 min using procedure 8, followed by aromatization with MnO_2 using procedure 7, gave 9-methoxy-5-methyl-4-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (**158**) (**XI**, X = Me, Y = phenyl), which was used directly.

Demethylation of **158** with BBr_3 using procedure 5 gave **11** (40% overall): mp 270−280 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.60 (s, 1H), 10.82 (s, 1H), 9.22 (s, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.47−7.42 (m, 4H), 7.36−7.23 (m, 2H), 7.06 (dd, J = 8.7, 2.0 Hz, 1H), 2.32 (s, 3H). EIMS found M^+, 342.1005; $C_{21}H_{14}N_2O_3$ requires 342.1004.

5-Methoxy-2-vinyl-1*H*-indole (159). Reaction of **106** with methyl(triphenyl)phosphonium bromide and LDA using procedure 11 gave **159** (**X**, X = Y = H) (87%): mp 80−81 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.09 (s, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.75−6.66 (m, 2H), 6.37 (s, 1H), 5.76 (d, J = 17.3 Hz, 1H), 5.21 (d, J = 11.6, 1H), 3.73 (s, 3H). Anal. ($C_{11}H_{11}NO$) C, H, N.

9-Methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (160). Reaction of **159** with maleimide at 180 °C using procedure 8, followed by aromatization of the adduct with MnO_2 using procedure 7, gave **160** (**XI**, X = Y = H) (76%): mp 260−270 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.91 (s, 1H), 11.10 (s, 1H), 8.38 (d, J = 2.6 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 8.8, 2.6 Hz, 1H), 3.88 (s, 3H). Anal. ($C_{15}H_{10}N_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

9-Hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (4). Demethylation of **160** with BBr_3 using procedure 5 gave **4** (79%): mp 335−345 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.77 (s, 1H), 11.04 (s, 1H), 9.23 (s, 1H), 8.24 (d, J = 2.3 Hz, 1H), 7.75 (2d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.7 Hz, 1H), 7.05 (dd, J = 8.7, 2.3 Hz, 1H). Anal. ($C_{14}H_8N_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

1-(5-Methoxy-1*H*-indol-2-yl)-1-propanone (161). Reaction of 5-methoxy-1*H*-indole-2-carbaldehyde (**106**) with ethylmagnesium bromide and oxidation of the resulting alcohol with MnO_2 using procedure 10 gave **161** (**IX**, X = Et) (82%): mp 170−171.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.22 (d, J = 1.7 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 9.1, 2.4 Hz, 1H), 3.77 (s, 3H), 2.96 (q, J = 7.3 Hz, 2H), 1.13 (t, J = 7.3 Hz, 3H). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

5-Ethyl-9-hydroxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (12). Reaction of **161** with benzyltriphenylphosphonium bromide using procedure 11 gave 2-[(*E,Z*)-1-ethyl-2-phenylethenyl]-5-methoxy-1*H*-indole (**162**) (**X**, X = Et, Y = phenyl) (38%): mp 95−97 °C. Anal. ($C_{19}H_{19}NO$) C, H, N.

Reaction of **162** with maleimide at 180 °C, followed by aromatization of the crude adduct with MnO_2 using procedures 8 and 7, gave 5-ethyl-9-methoxy-4-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (**163**) (**XI**, X = Et, Y = phenyl) (68%): mp 301−303 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.78 (s, 1H), 10.87 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.48−7.41 (m, 3H), 7.32−7.30 (m, 2H), 7.23 (dd, J = 8.8, 2.6 Hz, 1H), 3.89 (s, 3H), 2.76 (q, J = 7.4 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H).

Demethylation of **163** with BBr_3 using procedure 5 gave **12** (97%): mp 190−196 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.63 (s, 1H),

10.81 (s, 1H), 9.21 (s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.48−7.40 (m, 4H), 7.31−7.29 (m, 2H), 7.06 (dd, J = 8.7, 2.4 Hz, 1H), 2.74 (q, J = 7.4 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H). Anal. ($C_{22}H_{16}N_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

5-Methoxy-2-[(1*E*)-1-phenyl-1-propenyl]-1*H*-indole (164). Reaction of **166** (see later) with ethyl(triphenyl)phosphonium bromide and LDA using procedure 11 gave **164** (**X**, X = phenyl, Y = Me) (72%): mp 128−130 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.97 (s, 1H), 7.47−7.39 (m, 3H), 7.28−7.19 (m, 3H), 6.88 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 8.7, 2.4 Hz, 1H), 6.38 (q, J = 6.9 Hz, 1H), 5.69 (s, 1H), 3.69 (s, 3H), 1.67 (d, J = 6.9 Hz, 3H). Anal. ($C_{18}H_{17}NO$) C, H, N.

9-Methoxy-4-methyl-5-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (165). Reaction of **164** with maleimide using procedure 8, followed by aromatization with MnO_2 using procedure 7, gave **165** (**XI**, X = phenyl, Y = Me) (74%): mp 284−286 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.06 (br s, 1H), 10.93 (s, 1H), 8.43 (d, J = 2.6 Hz, 1H), 7.64−7.54 (m, 3H), 7.45−7.42 (m, 3H), 7.14 (dd, J = 8.9, 2.6 Hz, 1H), 3.32 (s, 3H), 2.48 (s, 3H). Anal. ($C_{22}H_{16}N_2O_3 \cdot {}^1/_3H_2O$) C, H, N.

9-Hydroxy-4-methyl-5-phenylpyrrolo[3,4-*c*]carbazole-1,3-(2*H*,6*H*)-dione (13). Demethylation of **165** with BBr_3 using procedure 5 gave **13** (85%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.01 (s, 1H), 10.79 (s, 1H), 9.17 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.34−7.60 (m, 2H), 7.57−7.52 (m, 1H), 7.43−7.41 (m, 2H), 7.34 (d, J = 8.7 Hz, 1H), 6.98 (dd, J = 8.7, 2.4 Hz, 1H), 2.26 (s, 3H). EIMS found M^+, 342.1003; $C_{21}H_{14}N_2O_3$ requires 342.1004.

(5-Methoxy-1*H*-indol-2-yl)(phenyl)methanone (166). Reaction of **106** with phenylmagnesium bromide and oxidation of the resulting alcohol with MnO_2 using procedure 10 gave **166** (**IX**, X = phenyl) (91%): mp 159−161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.86 (s, 1H), 7.94−7.91 (m, 2H), 7.71−7.66 (m, 1H), 7.61−7.57 (m, 2H), 7.42 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.03 (s, 1H), 6.99 (dd, J = 8.9, 2.4 Hz, 1H), 3.77 (s, 3H). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

2-[(*E*)-1,2-Diphenylethenyl]-5-methoxy-1*H*-indole (167). Reaction of **166** with benzyl(triphenyl)phosphonium bromide and LDA using procedure 11 gave **167** (**X**, X = Y = phenyl) (0.95 g, 73%): mp (DCM) 144−147 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.24 (s, 1H), 7.49−7.42 (m, 3H), 7.29−7.26 (m, 4H), 7.17−7.08 (m, 3H), 6.97−6.95 (m, 2H), 6.92 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.7, 2.4 Hz, 1H), 5.81 (s, 1H), 3.70 (s, 3H). Anal. ($C_{23}H_{19}NO \cdot {}^1/_{10}H_2O$) C, H, N.

9-Hydroxy-4,5-diphenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (14). Reaction of **167** with maleimide at 180 °C, followed by aromatization with MnO_2 using procedures 8 and 7, gave 9-methoxy-4,5-diphenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (**168**) (**XI**, X = Y = phenyl) (77%): ^{1}H NMR [$(CD_3)_2SO$] δ 11.08 (s, 1H), 11.02 (br s, 1H), 8.52 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.36−7.28 (m, 3H), 7.21−7.11 (m, 8H), 3.89 (s, 3H).

Demethylation of **168** with BBr_3 using procedure 5 gave **14** (87%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.96 (s, 1H), 10.94 (s, 1H), 9.23 (s, 1H), 8.37 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.35−7.29 (m, 3H), 7.22−7.10 (m, 7H), 7.03 (dd, J = 8.7, 2.4 Hz, 1H). Anal. ($C_{26}H_{16}N_2O_3$) C, H, N.

Methyl 2-(1-Phenylvinyl)-1*H*-indol-5-yl Ether (169). Reaction of **166** with methyl(triphenyl)phosphonium bromide and LDA using procedure 11 gave **169** (**X**, X = Ph, Y = H) (95%): mp 119−121 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.13 (s, 1H), 7.47−7.39 (m, 5H), 7.26 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.8, 2.4 Hz, 1H), 6.12 (s, 1H), 5.77 (s, 1H), 5.30 (s, 1H), 3.72 (s, 3H). Anal. ($C_{17}H_{15}NO$) C, H, N.

9-Methoxy-5-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (170). Reaction of **169** with maleimide at 180 °C using procedure 8, followed by aromatization of the adduct with MnO_2 using procedure 7, gave **170** (**XI**, X = Ph, Y = H) (73%): mp 281−285 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.63 (br s, 1H), 11.15 (br s, 1H), 8.45 (d, J = 2.5 Hz, 1H), 7.78−7.76 (m, 2H), 7.68 (s, 1H), 7.65−7.62 (m, 2H), 7.57−7.53 (m, 2H), 7.22 (dd, J = 8.8, 2.5 Hz, 1H), 3.89 (s, 3H). Anal. ($C_{21}H_{14}N_2O_3 \cdot {}^1/_3H_2O$) C, H, N.

9-Hydroxy-5-phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (15). Demethylation of **170** with BBr_3 using procedure 5 gave **15** (89%): mp 335−345 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.50 (s, 1H), 11.10 (s, 1H), 9.26 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 7.77−7.75 (m, 2H), 7.65−7.61 (m, 3H), 7.56−7.52 (m, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.06 (dd, J = 8.7, 2.4 Hz, 1H). Anal. ($C_{20}H_{12}N_2O_3$) H, N. C: calcd, 73.16; found, 72.71.

Procedures of Scheme 4. 1,9-Dihydroxy-4-phenyl-1,6-dihydropyrrolo[3,4-*c*]carbazol-3(2*H*)-one (16) and 3,9-Dihydroxy-4-phenyl-3,6-dihydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (19). $NaBH_4$ (four portions of 0.24 g, 0.025 mol total) was added over 5 h to a solution of **3**[11] (0.50 g, 1.50 mmol) in EtOH (80 mL), and the solution was left overnight. An additional four portions of $NaBH_4$ were added at 1 h intervals, and the solution was then diluted with water and extracted with EtOAc. The organic phase was dried and evaporated, and the residue was chromatographed on silica gel. Elution with EtOAc/petroleum ether (2:1) gave starting material (12 mg), followed by **19** (0.07 g, 14%): mp 300−310 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.26 (br s, 1H), 8.98 (s, 1H), 8.83 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 7.70 (br d, J = 7.0 Hz, 2H), 7.53 (s, 1H), 7.49−7.31 (m, 4H), 6.96 (dd, J = 8.7, 2.3 Hz, 1H), 6.25 (d, J = 9.7 Hz, 1H), 5.87 (d, J = 9.7 Hz, 1H). Anal. ($C_{20}H_{13}N_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

Elution with EtOAc gave a mixed fraction (0.014 g), followed by **16** (0.32 g, 64%): mp 300−310 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.38 (br s, 1H), 9.06 (s, 1H), 8.55 (br s, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 7.8, 2.1 Hz, 2H), 7.47−7.35 (m, 4H), 7.32 (s, 1H), 6.98 (dd, J = 8.6, 2.2 Hz, 1H), 6.38 (d, J = 10.3 Hz, 1H), 6.20 (d, J = 10.3 Hz, 1H). Anal. ($C_{20}H_{13}N_2O_3 \cdot H_2O$) C, H, N.

9-Hydroxy-1-methoxy-4-phenyl-1,6-dihydropyrrolo[3,4-*c*]carbazol-3(2*H*)-one (17). A solution of **16** (0.050 g, 0.16 mmol) and *p*-TsOH (15 mg) in MeOH (5 mL) was stirred at room temperature for 30 min and then poured into saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc, and the organic phase was dried and concentrated to dryness to give **17** (0.041 g, 74%): mp (EtOAc/petroleum ether) 290−300 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.47 (br s, 1H), 9.15 (br s, 1H), 8.75 (s, 1H), 7.57−7.53 (m, 3H), 7.44−7.37 (m, 4H), 7.36 (s, 1H), 7.09 (dd, J = 8.7, 2.4 Hz, 1H), 6.26 (s, 1H), 3.25 (s, 3H). Anal. ($C_{21}H_{15}N_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

9-Hydroxy-4-phenyl-1,6-dihydropyrrolo[3,4-*c*]carbazol-3(2*H*)-one (18). A solution of **16** (0.20 g, 0.605 mmol) in THF (30 mL) was treated sequentially with *p*-TsOH (23 mg, 0.121 mmol) and PhSeH (1.48 mL, 4.24 mmol), and the solution was stirred at room temperature for 1 h. The mixture was partitioned between water and EtOAc, and the organic layer was washed with aqueous $NaHCO_3$ solution. The organic phase was dried and evaporated, and the residue was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) and then EtOAc followed by EtOAc/MeOH (95:5) gave **18** (0.174 g, 91%): mp 270−280 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (br s, 1H), 9.13 (br s, 1H), 8.27 (br s, 1H), 7.60−7.52 (m, 2H), 7.47−7.36 (m, 4H), 7.34−7.31 (m, 1H), 7.30 (s, 1H), 6.99 (dd, J = 8.6, 2,2 Hz, 1H), 4.78 (br s, 2H). Anal. ($C_{20}H_{14}N_2O_2 \cdot {}^1/_4H_2O$) C, H. N: calcd, 8.78; found, 8.37.

Procedures of Scheme 5. 4-(2-Chlorophenyl)-9-methoxy-4,5,6,10c-tetrahydro-1*H*-furo[3,4-*c*]carbazole-1,3(3a*H*)-dione (114). A solution of **113** (0.30 g, 1.06 mmol) and maleic anhydride (0.16 g, 1.59 mmol) in xylene (30 mL) was heated at reflux for 18 h, then concentrated under reduced pressure and chromatographed on silica gel. Elution with EtOAc/hexane (1:2) gave **114** (0.29 g, 72%): mp (EtOAc/hexane) 189−191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.16 (br s, 1H), 7.69 (dd, J = 7.7, 1.4 Hz, 1H), 7.51 (dd, J = 7.7, 1.4 Hz, 1H), 7.43 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.36 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.6, 2.4 Hz, 1H), 4.70 (d, J = 7.7 Hz, 1H), 4.47 (dd, J = 7.7, 3.5 Hz, 1H), 3.78 (s, 3H), 3.71−3.66 (m, 1H), 3.36 (dd, J = 15.9, 13.0 Hz, 1H), 2.99 (dd, J = 15.9, 4.1 Hz, 1H). Anal. ($C_{21}H_{16}ClNO_4$) C, H, N.

4-(2-Chlorophenyl)-2-(2,4-dimethoxybenzyl)-9-methoxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (115). A solution of anhydride **114** (2.80 g, 7.42 mmol) in acetic acid (70 mL) was treated

with 2,4-dimethoxybenzylamine (1.67 mL, 11.1 mmol), and the resulting solution was heated at reflux for 6 h, then partially concentrated under reduced pressure and diluted with water. The precipitate was collected by filtration, washed with water and dried, then aromatized in dioxane with MnO_2 using procedure 7. The product was chromatographed on silica gel, eluting with EtOAc/hexane (1:1), to give **115** (1.46 g, 37%): mp (MeOH) 224−226 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.02 (br s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 7.62 (s, 1H), 7.58 (m, 2H), 7.53−7.42 (m, 3H), 7.25 (dd, J = 8.8, 2.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.45 (dd, J = 8.4, 2.3 Hz, 1H), 4.68 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H). Anal. ($C_{30}H_{23}ClN_2O_5$) C, H, N.

Array Synthesis of N6-Substituted Analogues of Table 4 from 115. To a solution of carbazole **115** (50 mg, 0.09 mmol per reaction) in dimethylformamide (5 mL) under nitrogen were added potassium carbonate (0.13 g, 0.93 mmol) and alkyl halide (0.28 mmol). The resulting suspension was warmed to 90 °C with stirring for 3 h before being diluted with water and extracted with ethyl acetate. The organic phase was dried, the drying agent was removed, and the solution was concentrated to dryness to give alkylated carbazole (**XIII**), which was used directly.

A solution of the crude carbazole **XIII** from the above step (0.09 mmol) in anisole (0.5 mL) and TFA (2.0 mL) was heated in a sealed vessel at 90 °C for 18 h, and then solvent was removed under reduced pressure. The residue was diluted with water and extracted with Et_2O (3×). The combined organic extracts were washed with 1 N KOH and brine, then dried, and evaporated. The aqueous layer was acidified with concentrated HCl and extracted with Et_2O, and the organic extract was evaporated. The combined crude material was triturated with Et_2O/hexane and then dissolved in DCM (20 mL) and demethylated with BBr_3 as described in procedure 5. Chromatography of the product on silica gel, eluting with EtOAc/hexane (1:1 to 1:0), gave the compounds of Table 4 as yellow solids. The products were characterized by HPLC−MS analysis.

The following compounds were prepared by the above-described general method.

4-(2-Chlorophenyl)-9-hydroxy-6-methylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (25). 25 was prepared from **115** and MeI. Found: M + H = 377. Purity 100%.

4-(2-Chlorophenyl)-6-ethyl-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (100). 100 was prepared from **115** and EtI. Found: M + H = 391. Purity 97%.

4-(2-Chlorophenyl)-9-hydroxy-6-propylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (101). 101 was prepared from **115** and *n*-PrBr. Found: M + H = 405. Purity 99%.

4-(2-Chlorophenyl)-9-hydroxy-6-isopropylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (102). 102 was prepared from **115** and *i*-PrBr. Found: M + H = 405. Purity 99%.

6-Butyl-4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (103). 103 was prepared from **115** and *n*-BuBr. Found: M + H = 419. Purity 98%.

4-(2-Chlorophenyl)-9-hydroxy-6-isopentylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (104). 104 was prepared from **115** and isopentyl bromide. Found: M + H = 433. Purity 98%.

4-(2-Chlorophenyl)-9-hydroxy-6-pentylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (105). was **105** prepared from **115** and pentyl bromide. Found: M + H = 433. Purity 98%.

Determinations of Enzyme Inhibition. Wee1 Inhibition. The assay was carried out in 96-well filter microtiter plates (Millipore; MADP NOB 10). Compounds were dissolved and diluted in DMSO. Then 10 μL of 3× EDB buffer (150 mM Tris, pH 8.0, 30 mM NaCl, 30 mM $MgC1_2$, 3 mM DTT), 18 μL of water, and 2 μL of drug dilution were added to the test wells and mixed thoroughly. An amount of 10 μL of enzyme−substrate mixture was added to the wells. The Wee1 enzyme (human Wee1 kinase aa 215−647, Onyx Pharmaceuticals, expressed in and purified from a baculovirus protein expression system) concentration was 0.01 μg/μL, and the substrate (polyornithine/tyrosine (4: 1), Sigma Chemical Co.) was 0.6 μg/μL in 1× EDB buffer. The plates were mixed thoroughly for 5 min at room temperature. The reaction was started by adding 10 μL of 1× EDB buffer containing 47.5 μM ATP (Sigma) and 0.026 μCi/pL γ-^{32}P-ATP (ICN Biomedicals, Inc.). The plates were mixed at room temperature for 20 min. The reaction was stopped by adding 50 μL of ice-cold 20% TCA with 0.1 M tetrasodium pyrophosphate. Plates were incubated on ice or refrigerated at 4 °C for 1 h. The liquid reaction mixture was removed on a vacuum manifold, and the precipitated phosphorylated substrate was rinsed five times with 200 μL of ice-cold 10% TCA with 0.1 M tetrasodium pyrophosphate. An amount of 25 μL of liquid scintillation cocktail was added to the membrane bound substrate, and the plate was read in a Microbeta plate reader (Perkin-Elmer). Activity of compounds was calculated in comparison to uninhibited control determinations in each assay.

Chk1 Inhibition. The assay was carried out in round-bottom polypropylene 96-well plates (Costar). Compounds were tested in serial dilutions beginning with a high concentration of 50 μM followed by up to nine 3-fold dilutions. Compounds were dissolved and diluted in DMSO. An amount of 2 μL of drug was spotted on the bottom of the assay plates, then diluted with 58 μL of Chk1 buffer (20 mM Tris, pH 8.0, 50 mM NaCl, 10% glycerol, 10 mM $MgCl_2$, 5 mM dithiothreitol), and mixed at room temperature for 1 min. An amount of 20 μL of buffer containing 250 ng/well Chk1 enzyme (Onyx Pharmaceuticals) and 1 μg/well GST-Cdc25 substrate (Onyx Pharmaceuticals) was added. Contents of the wells were mixed for 1 min and incubated at room temperature for 10 min. Then 20 μL of buffer containing 20 μM ATP and 0.4 μCi ATP [γ-^{33}P] was added. The contents were mixed for 1 min and incubated at 30 °C for 30 min. The reaction was stopped by the addition of 50 μL of 120 mM EDTA to each well except to the control wells already containing EDTA. Then 140 μL of the contents of the wells was transferred to the wells of Reacti-Bind glutathione coated 96-well plates (Pierce). Contents were mixed for 1 min and incubated at room temperature for 1 h. All of the wells were rinsed three times each with 300 μL of PBS and air-dried. Then 200 μL of MicroScint (Packard) was added to the wells. Plates were sealed with an adhesive cover and counted in a TopCount microplate scintillation counter (Packard). Activity of the compounds was calculated by comparison to uninhibited control determinations in each assay.

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Supporting Information Available: Additional experimental procedures and characterizations; combustion analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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