Synthesis of Pyrroloquinolines as Indole Analogues of Flavonols

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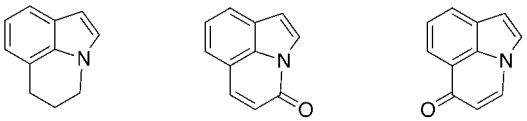
7-Acetyl-4,6-dimethoxy-3-phenylindole **10** was converted into a range of 7-indolyl chalcones **13** by reaction with aryl aldehydes under basic conditions. Oxidation of the chalcones **13** with alkaline hydrogen peroxide gave the isolable epoxides **14**, which were cyclized with further base treatment into the indole flavonols, or 5-hydroxy-6-oxopyrroloquinolines **15**. The related compounds **25** and **26**, examples of indole flavanones and flavones, respectively, were also synthesized. UV spectroscopic comparisons between flavonoids and indole flavonoids are discussed.

Introduction

Pyrrolo[3,2,1-*ij*]quinoline systems, such as that shown by the reduced structure **1**, have been found in nature and their synthesis and reactions have been reviewed.[1] Compounds of this class, and especially the hexahydropyrroloquinolines **1**, show a wide range of biological activity.[2,3]

Pyrroloquinolines also exist in a variety of oxidized forms, especially the 4- and 6-oxo-pyrroloquinolines **2** and **3**, respectively.[1] Some 4-oxopyrroloquinolines **2** have been found to induce the reversible inhibition of fertility in male rats.[4−6] The reduced compound lycorine acts against tumor cells and inhibits protein and DNA synthesis.[4] As yet there appears to be no report of any naturally occurring 6-oxopyrroloquinoline. Synthetic 6-oxopyrroloquinolines **3** utilize one of two general approaches, involving either the construction of a pyrrole ring on to a quinoline by a standard indole synthesis,[7−14] or the construction of a new six-membered ring between N1 and C7 of an indole.[1,15−22]



1 **2** **3**

Synthesis of both natural and unnatural flavonoids have been widely studied because of their extensive biological properties.[23−32] Incorporation of the indole nucleus within the flavonoid structure leads to 6-oxopyrroloquinolines, which could be derived from indoles. A similar comparison of flavanones and 2-aryl-1,2,3,4-tetrahydro-4-quinolones has been considered previously.[33,34] This synthetic prospect has been made accessible by the development of electron-rich 4,6-dimethoxyindoles which are activated at C7, thus providing a wide extension of the chemistry that can occur at that position, including the possibility of cyclization between C7 and N1.[35−37] In particular traditional flavonoid synthetic routes can be employed with such systems.

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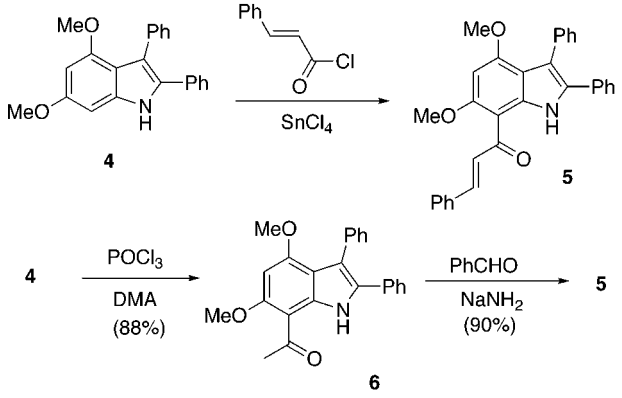
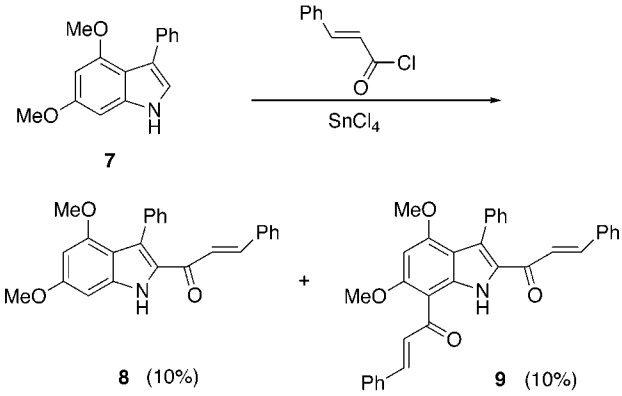
Scheme 1



Scheme 2

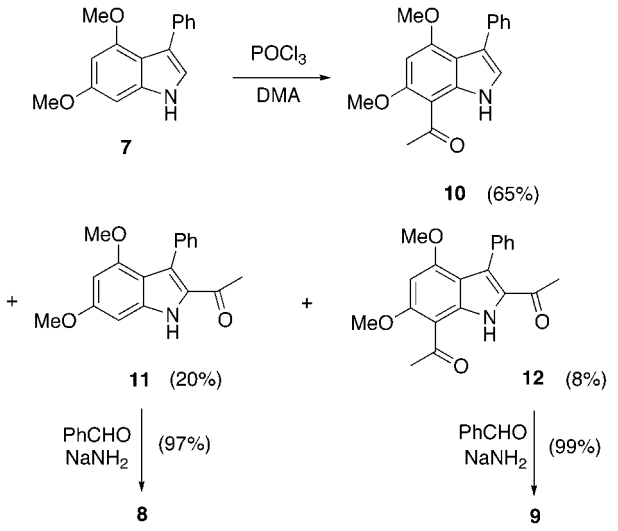


Results and Discussion

Most flavonoid syntheses use the requisite chalcone either as an immediate precursor or as an unisolated intermediate en route to the cyclic flavonoids.[23−25] It was therefore essential to obtain the indole analogues of the chalcones, namely the 7-cinnamoylindoles. Such materials would provide a new synthetic approach to the construction of 6-oxopyrroloquinolines **3** and also extend the chemistry of electron-rich indole systems.

The 7-cinnamoylindole **5** has been prepared from 4,6-dimethoxy-2,3-phenylindole **4** by direct Friedel−Crafts acylation using cinnamoyl chloride and stannic chloride in benzene (Scheme 1).[38,39] Acetylation has been previously carried out on the 2,3-diphenylindole **4** either via a modified Vilsmeier−Haack acetylation in 88% yield or a Friedel−Crafts acylation in 50% yield.[38] Acylation of 4,6-dimethoxy-3-phenylindole **7**[37] with cinnamoyl chloride and stannic chloride in toluene did not yield the desired 7-cinnamoylindole but instead gave the 2-cinnamoylindole **8** and the 2,7-bis-(cinnamoyl)indole **9** in 10% yield each (Scheme 2). The alternative aldol approach was therefore investigated. Acetylation of indole **7** utilizing *N*,*N*-dimethylacetamide and phosphoryl chloride gave the 7-acetylindole **10** in 65% yield, the 2-acetylindole **11** in 20% yield, and the 2,7-diacetylindole **12** in 8% yield (Scheme 3).

Scheme 3



Condensation of the 7-acetylindole **10** with a variety of substituted benzaldehydes gave a range of new indol-7-yl chalcones **13a**−**d**, in yields of 58−95%. A similar reaction with cinnamaldehyde gave the corresponding diene analogue **13e** (Scheme 4). The 2-acetylindole **11** and 2,7-diacetylindole **12** were also readily condensed with benzaldehyde to produce the same products, **8** and **9**, that were obtained from the Friedel−Crafts acylation with cinnamoyl chloride, but this time in almost quantitative yield (Scheme 3). The ^{1}H NMR spectra of the cinnamoyl compounds showed a characteristic set of AB doublets ranging between 7.74 and 8.04 ppm for the olefinic protons H3 and H2; the coupling constant was 16 Hz and indicative of trans geometry.

Flavonols. The two most common methods for the cyclization of the indole chalcones are the Rasoda reaction, the base-catalyzed cyclization of chalcone dibromides and bromohydrins,[40,41] and the Algar−Flynn−Oyamada reaction, the alkaline hydrogen peroxide oxidation of the chalcone.[42−45] Numerous other methods exist and new ones continue to appear in the literature.[46] The Rasoda method was not attempted since indole **4** is susceptible to bromination at C2, so the latter was chosen. The Algar−Flynn−Oyamada reaction is thought to proceed via an epoxide intermediate, though this has been the subject of debate for some time.[42,44] Oyamada initially proposed that the reaction proceeded via the flavanone, which was then oxidized at a later stage to the flavonol, in a fashion similar to the von Kostanecki synthesis of flavonol.[43] Algar and Flynn believed that either an epoxide or a glycol was formed initially, and this then underwent intramolecular cyclization to give

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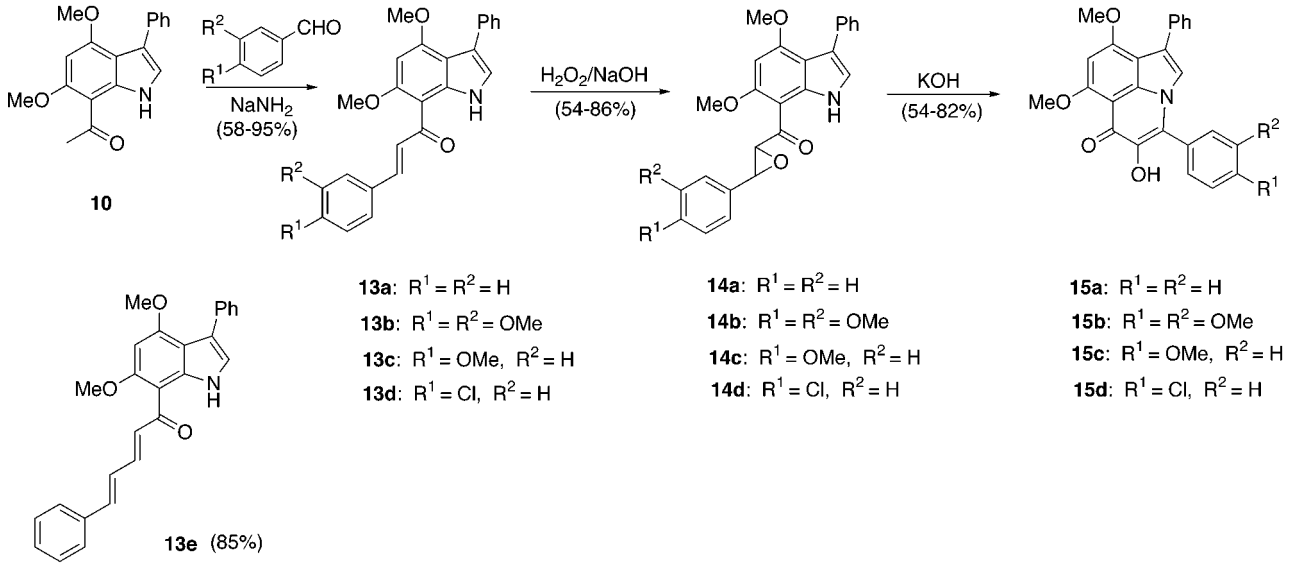
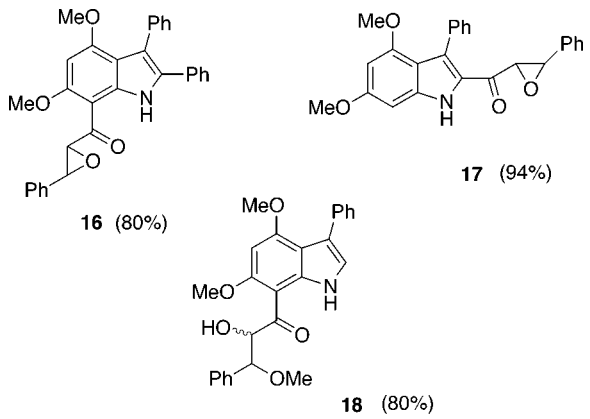
Scheme 4



the flavonol.[42] Further investigations of the reaction by Geissman and Fukushima[45] revealed that the type of product depended on the chalcone substrate. Certain chalcones gave the flavonol, while others gave aurones, otherwise known as benzal-coumarones, and in some cases a mixture of both flavonol and aurone was obtained. The product was found to be somewhat dependent on the type and position of substituents on the 2-hydroxy chalcone.[42,45] These results gave more concrete evidence for the existence of an epoxide intermediate, with flavonols forming from attack upon the β-carbon of the epoxide and aurones resulting from attack upon the α-carbon of the epoxide. Interestingly, no trace of a chalcone epoxide was ever isolated from these reactions.[45] However, if the 2′-hydroxy group of chalcone was replaced with a methoxy group, then the same conditions readily yielded only the epoxide of the chalcone.[47] More recently dimethyldioxirane has been used to prepare a series of chalcone epoxides from a range of chalcones.[48,49] The C2 position of indole **7** was likely to be susceptible to oxidation by both peracids and dimethyldioxirane.[50,51]

Reaction of the chalcones **13a**−**d** in aqueous tetrahydrofuran with saturated sodium hydroxide and 30% hydrogen peroxide solution gave the corresponding epoxides **14a**−**d** in yields ranging from 54 to 94% (Scheme 4). Similarly, chalcone **5** yielded the epoxide **16**, and the 2-cinnamoyl indole **8** gave the epoxide **17**. Once isolated, these epoxides were surprisingly stable, as were those chalcone epoxides made by Patonay, Toth, and Adam.[48] The ^{1}H NMR spectra of these compounds showed a downfield shift for the signals of H3 and H2, which ranged between 3.32 and 4.5 ppm, with a coupling constant of 2 Hz indicative of a trans-disubstituted epoxide. However, the indol-7-yl chalcone epoxide **14a** underwent a facile ring-opening reaction in acidic methanol to yield the methoxy alcohol **18**.



Patonay, Toth, and Adam used a variety of bases such as tetrabutylammonium hydroxide, triethylamine, and (dimethylamino)pyridine to cyclize their epoxides to give benzyl coumaranones and dihydroflavonols.[48] The cyclization of these epoxides in base to give dihydroflavonols provided good evidence that the Algar−Flynn−Oyamada reaction does indeed proceed via the unisolated epoxide to give dihydroflavonols and flavonols.

The indole epoxides **14a**−**d** were cyclized with potassium hydroxide in aqueous tetrahydrofuran yielding the bright yellow indole flavonols or 6-oxopyrroloquinolines **15a**−**d** in yields ranging from 54 to 82% (Scheme 4). In contrast, the 2,3-diphenylindole-7-cinnamoyl epoxide **16** failed to give either the expected 6-oxopyrroloquinoline product **19** or the isomeric aurone analogue **20** (Scheme 5). It is assumed that in this case the steric hindrance resulting from the buttressing of the adjacent phenyl groups prevents cyclization. Because of the steric interference, this example more than any other offered encouragement for cyclization to be forced to proceed via attack at the α-carbon rather than the β-carbon of the epoxide to yield an aurone. However, this did not occur, and consequently it is noteworthy that this general cyclization reaction exclusively produces the flavonol analogue rather than the aurone analogue, especially

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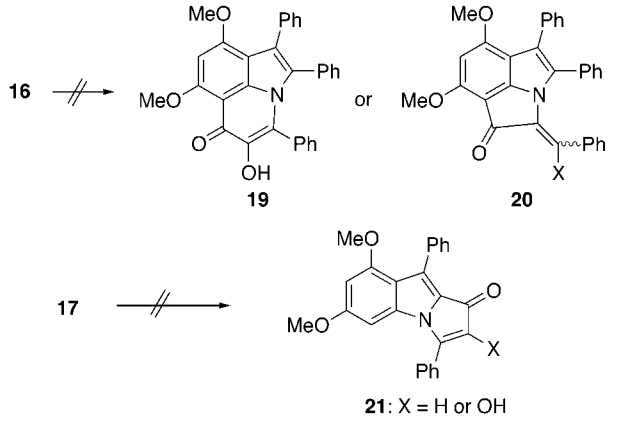
Scheme 5



since the same substitution pattern of methoxy groups on the simple chalcones favors aurone formation.[42,45] It would appear that in this case, attack at the β-carbon of the epoxide is exclusively favored over attack at the α-position. This outcome is not surprising when it is considered that each of the possible products contains three fused rings. However, the favored six−six−five-membered ring flavone-analogue product would be substantially less strained than the alternative six−five−five-membered ring aurone-analogue product. Furthermore, the indole-2-cinnamoyl epoxide **17** failed to produce an indole pyrrolone **21** and instead yielded a mixture of decomposition products (Scheme 5).

A more detailed mechanism for the cyclization of **14** to **15** presumably involves deprotonation of the indole nitrogen of compound **14** followed by attack of the nitrogen anion on the epoxide ring to give the anion of the indole dihydroflavonol **22** (Scheme 6). The cyclization then proceeds beyond the indole dihydroflavonol, possibly via an enolized diketone **23** right through to the indole flavonol **15**. It is assumed that the dihydroflavonol **22** forms during the reaction but then undergoes oxidation in the air to give the flavonol **15**. The dependence of the reaction on oxygen was demonstrated by experiments showing that substantially shorter times were required for reaction completion when air was bubbled through the reaction mixture.

It is interesting to note that the same conditions required for the Algar−Flynn−Oyamada reaction when applied to the indole chalcones **13** result only in epoxidation and not cyclization. It is presumed that the NH of the indole epoxide is less acidic than the OH of the chalcone epoxides and therefore requires either a stronger base or a longer reaction time to produce the anion. Closer examination of the epoxidation reaction mixtures, in which the reaction had been allowed to proceed for an extended period, showed traces of the indole flavonol product. This observation also supports the proposed mechanism of the Algar−Flynn−Oyamada reaction.

There were significant aspects of the spectral data that were characteristic for these compounds **15**, most notably the absence of an indole NH peak in both ^{1}H NMR and IR spectra, confirming that cyclization had indeed occurred at this position. The epoxide proton and carbon resonances were absent from both ^{1}H and ^{13}C NMR spectra and a new proton peak at ∼6.60 ppm was identified as the new H8 of the pyrroloquinoline. It was difficult to assign unequivocally a signal for the hydroxyl proton at C5 in either the ^{1}H NMR or IR spectra. It is probable that the hydroxyl group is strongly hydrogen bonded to the adjacent carbonyl group, which appears at around 1610 cm^{-1} in the IR spectra and is in most cases too broad to be seen in either the ^{1}H NMR or IR spectra. The IR spectra of these compounds revealed a very small absorption consistent with a hydroxyl group of this nature. However, mass spectroscopy confirmed the correct mass for these compounds and supported the presence of the hydroxyl group.

The existence of the hydroxyl group at C5 was further proven by the derivatization of the indole flavonol **15a** through acetylation with acetic anhydride to give the unstable acetate **24**, which although characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectroscopy was found to be susceptible to hydrolytic degradation over time (Scheme 7). Like the true flavonols, the indole flavonols display a bright orange phosphorescence under long wave UV radiation. Acetylation of the hydroxyl group at C5 cancels the contribution of the hydroxyl group, altering the bright blue phosphorescence to a brilliant blue. The acetylated indole flavonols thus display a phosphorescence similar to that found for the indole flavones. A similar effect is observed in flavonols when the equivalent hydroxyl group is acetylated.[52]

Flavanones. Flavanones, the 2,3-dihydro derivatives of flavones, form the central intermediates from which most, if not all, other natural flavonoids originate.[23] They often occur with the corresponding flavones, but generally in heartwoods, barks, roots, and to a lesser extent leaves and petals, thus demonstrating the tendency for the oxidation state of flavonoids to increase in the upper extremities of a plant.[24,25] Flavanones are isomeric with chalcones, and the two species readily undergo interconversion, with acid favoring ring closure and base favoring chalcones.[24,25] Most methods for the synthesis of flavanones utilize either the cyclization of a chalcone[53−55] or the hydrogenation of a flavone.[56,57] Analogous to these conversions, the base-catalyzed isomerization of 2-amino chalcones gives the corresponding tetrahydro-4-quinolones.[58]

Indole chalcones readily undergo intermolecular Michael addition,[38,39,59−61] and intramolecular addition of the indole anion should yield the indole flavanones. When the two representative indole chalcones **13a** and **13b** were further treated with sodium hydride in tetrahydrofuran under reflux, the indole flavanones **25a** and **25b** were formed respectively in moderate yield (Scheme 8). These compounds **25a** and **25b** displayed a pale blue phosphorescence under UV light, as do the simple flavanones. The benzylidene compound **27** was further prepared by base-catalyzed reaction of compound **25a** with benzaldehyde (Scheme 9). Similar benzylidene

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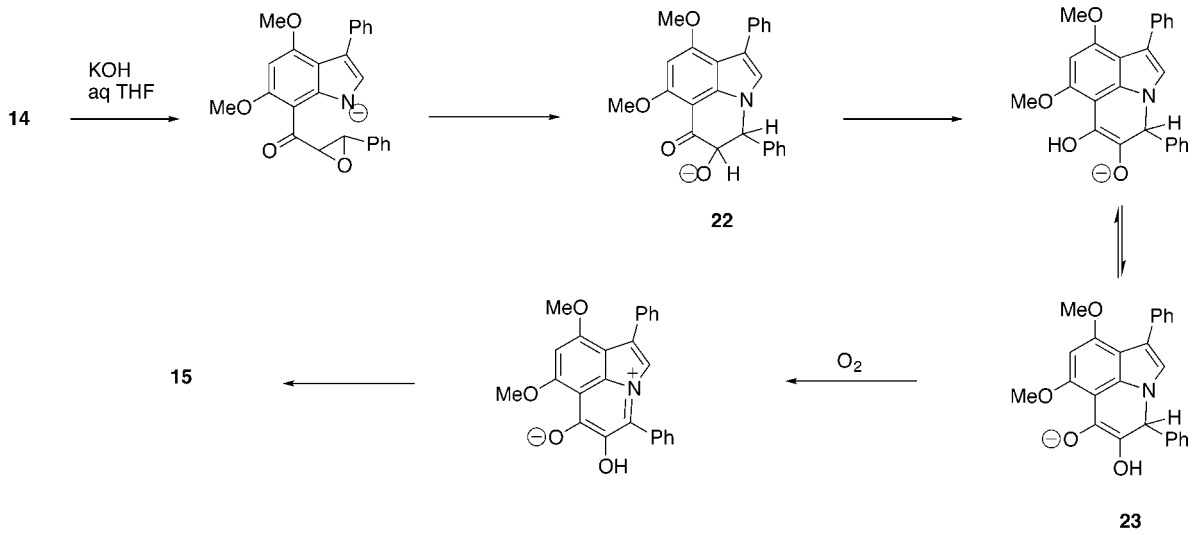
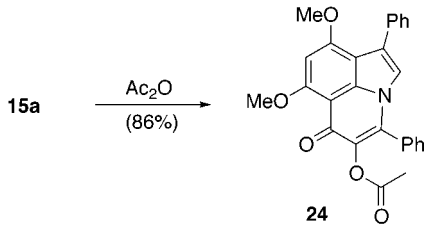
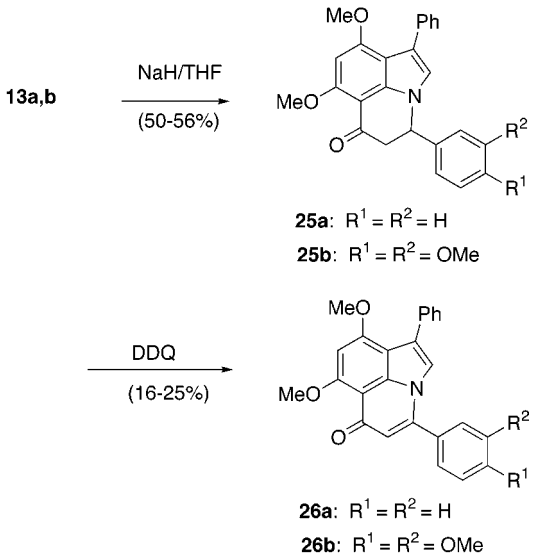
Scheme 6



Scheme 7



Scheme 8



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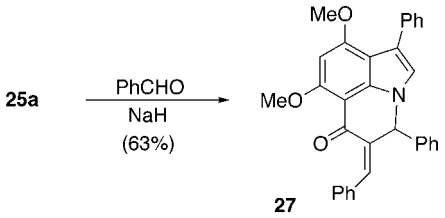

compounds have been made from flavanones and chromones through either acid- or base initiated-condensations with benzaldehydes.[62,63] The ^{1}H NMR spectra for compounds **25** showed characteristic splitting patterns for H4 and H5: compound **25b** showed an ABX pattern, but the accidental equivalence of the 5-protons in compound **25a** led to a simple AB system.

Flavones. Flavones, particularly those substituted with methoxy groups, are widespead among plants.[24] Their biochemical role is unclear, but it has been suggested to be that of a natural fungicide.[64] They can be synthesized by cyclization of dibromo chalcones[65,66] or β-diketones,[67,68] or by the oxidation of flavanones with selenium dioxide[23] or their dehydrogenation using palladium in *n*-octadecanol.[70] Previous synthesis of 6-oxopyrroloquinolines was effected by the acid-catalyzed cyclization of indole β-diketones.[22] However, given the availability of the indole flavanones **25a** and **25b**, dicyanodichloroquinone (DDQ) was used to oxidize them to the indole flavones **26a** and **26b** although in yields of only 16−25% (Scheme 8). These compounds showed less complex ^{1}H NMR spectra, with H5 appearing as a singlet in the region 6.40−6.60 ppm. Under UV light, these compounds displayed a brilliant blue phosphorescence, similar to that displayed by the flavones, but more intense than that displayed by the flavanones and their indole analogues.

Comparison of UV Spectra of Pyrroloquinolines and Their Related Flavonoids. The UV spectrum of the unsubstituted indole nucleus contains a peak at 216 nm (assigned as β-bands) and a wide absorption between 260 and 290 nm (assigned as 260 nm for the ρ-bands and 287 nm for the α-bands).[71] That of 4,6-dimethoxy-3-phenylindole **7** shows similar absorptions which display

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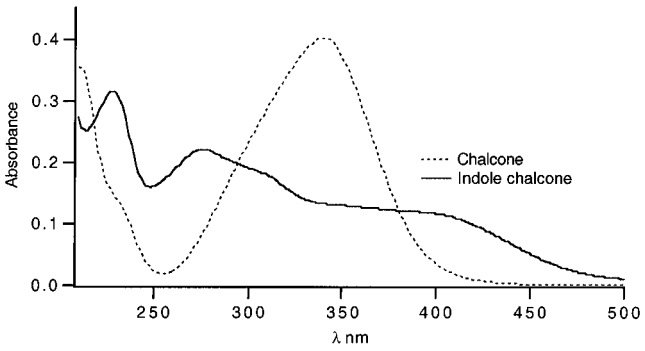

Figure 1. Comparison of UV spectra of 4′,6′-dimethoxy-2′-hydroxy chalcone with its indole chalcone analogue **13a**.

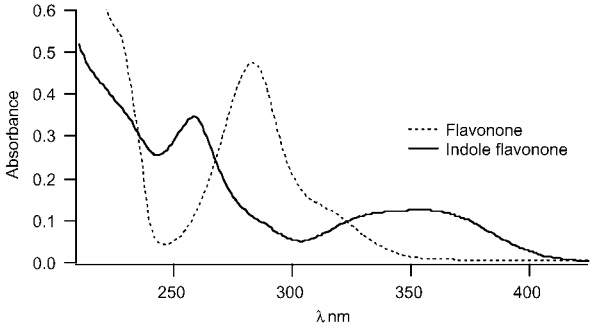

Figure 2. Comparison of UV spectra of 5,7-dimethoxy-2-phenylflavanone with its indole flavanone analogue **25a**.

a slight bathochromic shift in all bands. The addition of further conjugation provided by the acetyl group increases the shift of these bands in the spectrum of compound **10**.[71] The UV spectra of flavonoids show two distinct band regions corresponding to the cinnamoyl component (Band I, 300−380 nm) and the phenolic component (Band II, 240−280 nm).[23,24,72]

Chalcones. Polyhydroxy chalcones absorb strongly in Band I and less strongly in the Band II region, with further hydroxy or methoxy substitution resulting in a bathochromic shift in the relevant band of the affected chromophore.

The UV spectrum of the indole chalcone **13a** possesses little similarity with that of the phenol analogue 4′,6′-dimethoxy-2′-hydroxy chalcone, extending further into the visible region and containing many more absorption maxima. The maximum at 397 nm, most probably due to the cinnamoyl chromophore and related to Band I, has experienced a bathochromic shift of some 57 nm from that of the parent chalcone, possibly because of the increase in conjugation arising from the indole nucleus (Figure 1).

Flavanones. Flavanones do not show the conjugation between the B ring and the carbonyl group so absorb at comparatively shorter wavelengths. The major absorbance appears for Band II in the 270−290 nm region and Band I generally appears as a low intensity inflection between 320 and 330 nm. The spectrum of the indole flavanone **25a** contained two strong maxima at 258 and 353 nm, unlike that of its flavanone analogue (Figure 2), and showed more in common with the spectrum of the 7-acetyl indole **10**.

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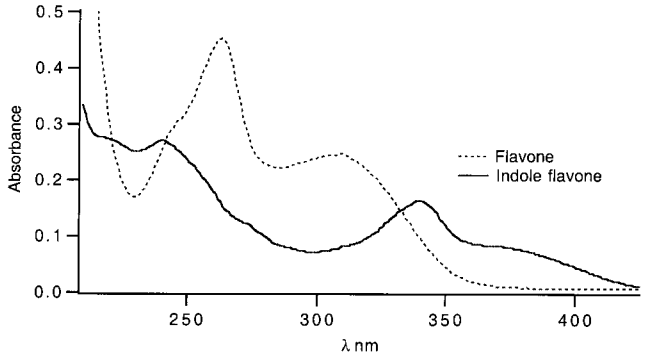

Figure 3. Comparison of UV spectra of 5,7-dimethoxy-2-phenylflavone with its indole flavone analogue **26a**.

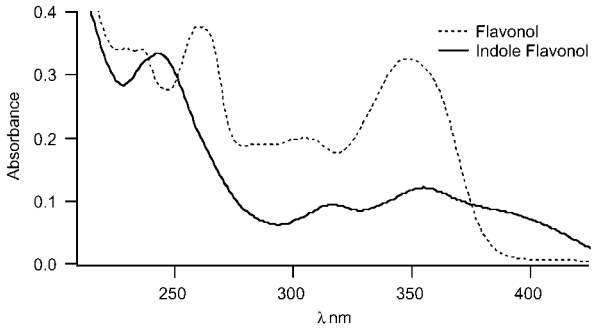

Figure 4. Comparison of UV spectra of 5,7-dimethoxy-2-phenylflavonol with its indole flavonol analogue **15a**.

Flavones and Flavonols. Flavones and flavonols generally exhibit high-intensity Band II maxima between 240 and 270 nm and Band I maxima between 320 and 380 nm. The position of Band I becomes important in distinguishing between flavones and flavonols. Band I appears for flavones between 304 and 350 nm and for flavonols between 352 and 385 nm, the bathochromic shift being attributed to the effect of the hydroxyl group at position-3.[23,24] The spectrum of the indole flavone **26a** contained a maximum at 340 nm assigned as the Band I equivalent and bathochromically shifted by approximately 34 nm from that of the simple flavone analogue (Figure 3). The spectrum of the indole flavonol **15a**, showed the greatest similarity with that of its flavonoid analogue. Apart from a maximum at 243 nm attributed to the indole nucleus, there were two maxima at 317 and 356 nm of similar shape and position to Band I of the simple flavonol, the spectrum of which gave maxima at 261 nm for Band II and at 349 nm for Band I. At the base of the Band I equivalent, an inflection extended further into the visible region, as a consequence of other conjugation within the pyrroloquinoline ring (Figure 4).

Clearly there are certain similarities between the indole flavonoid analogues or pyrroloquinolines and the flavonoids themselves. These similarities are attributed to the presence of the cinnamyol component common to both species and evident as long as the conjugation associated with this component remains intact. These comparisons are dependent upon the cinnamoyl component being part of a ring system, and the similarity increases with the increase in the oxidation state of this moiety. This is most noticeable in the comparison of the indole flavonols with the simple flavonols.

Conclusions

The replacement of phenols by suitably activated indoles enables the adaptation of flavonoid syntheses to generate a new range of pyrroloquinolines, which serve as indole analogues of flavonoids. While similar synthetic approaches can be used, there are some significant differences in the regiochemistry involved and also in the stability of some intermediates. A consideration of UV spectra also highlights similarities and differences in the two systems.

Experimental Section

General Information. ^{1}H NMR spectra were recorded at 300 MHz or at 500 MHz and refer to deuteriochloroform solutions with chloroform (7.26 ppm) as an internal standard. Signals due to exchangeable protons (NH) were identified by exchange with deuterium oxide. ^{13}C NMR spectra were recorded at 125.77 MHz and refer to deuteriochloroform solutions with chloroform (77.0 ppm) as an internal standard. Low resolution mass spectra were obtained at 70 eV and 8000 V accelerating potential at 210 °C ion source temperature. Infrared spectra refer to paraffin mulls or KBr disks of solids. Ultraviolet spectra refer to solutions in absolute methanol. Microanalyses were performed by Dr. H. P. Pham of the UNSW Microanalytical Unit. Flash column chromatography was carried out using Merck silica gel 7736 60H, while thin-layer chromatography was performed on 3 mm plates using Merck silica gel 7730 60GF$_{254}$.

Synthesis of Indole Chalcones via Friedel−Crafts Acetylation. A solution of stannic chloride (1.13 g, 4.33 mmol) in anhydrous toluene (5 mL) was added dropwise with stirring into a solution of 4,6-dimethoxy-3-phenylindole **7** (0.88 g, 3.5 mmol) and cinnamoyl chloride (0.64 g, 3.8 mmol) in anhydrous toluene (25 mL) at 0 °C. The mixture was brought to room temperature and allowed to stir for 30 h. Ice−water was added, and the mixture was stirred at room temperature for 1 h, producing an insoluble precipitate. When made strongly alkaline with 10% sodium hydroxide solution, this formed an orange solution, which was extracted with dichloromethane and dried and the solvent reduced. The resultant orange solid was then purified via column chromatography (ethyl acetate/petroleum ether 30:70), and afforded two products.

(i) 1-(4,6-Dimethoxy-3-phenylindol-2-yl)-3-phenylprop-2-en-1-one (8). Orange prisms (0.13 g, 10%), mp 244−245 °C (dichloromethane/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.87 (s, 3H), 6.12 (d, *J* 1.5 Hz, 1H), 6.48 (d, *J* 1.5 Hz, 1H), 6.63 (d, *J* 15.9 Hz, 1H), 7.05−7.53 (m, 10H), 7.64 (d, *J* 15.4 Hz, 1H), 9.58 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.18, 55.58, 85.75, 93.08, 113.75, 124.0, 125.48, 127.34, 127.42, 128.15, 128.63, 129.87, 131.41, 132.30, 135.08, 135.86, 138.50, 140.74, 157.02, 161.17, 181.31; IR 3280 (br m), 1620 (m); UV 232 (18000), 279 (12000), 330 (11000), 407 (17000); MS 383 (M^+, 100). Anal. Calcd for $C_{25}H_{21}NO_3$ (383): C, 78.3; H, 5.8; N, 3.6. Found: C, 78.3; H, 5.5; N, 3.7.

(ii) 1-(4,6-Dimethoxy-(7-(3-phenylprop-2-en-1-one-3-phenylindol-2-yl))-3-phenyl-prop-2-en-1-one (9). Yellow powder (0.17 g, 10%), mp 217−219 °C (dichloromethane/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 4.07 (s, 3H), 6.17 (s, 1H), 6.57 (d, *J* 15.9 Hz, 1H), 7.04−7.63 (m, 15H), 7.63 (d, *J* 15.4 Hz, 1H), 7.80 (d, *J* 15.4 Hz, 1H), 7.93 (d, *J* 15.4 Hz, 1H), 11.54 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.39, 56.66, 88.12, 105.13, 113.67, 123.97, 127.50, 128.04, 128.12, 128.55, 128.77, 129.63, 131.30, 132.24, 135.05, 135.51, 135.89, 138.87, 140.95, 141.0, 161.60, 163.17, 181.23, 188.77; IR 3400 (m), 1640 (m); UV 222 (18200), 321 (14000), 370 (22200); MS 515 (M^+, 14). Anal. Calcd for $C_{34}H_{27}NO_4$ (515): C, 79.5; H, 5.3; N, 2.7. Found: C, 79.9; H, 5.5; N, 2.7.

Acetylation of 4,6-Dimethoxy-3-phenylindole (7). Phosphoryl chloride (10.52 g, 68.6 mmol) was added slowly to a stirred ice-cold solution of indole **7** (2.48 g, 9.8 mmol) in dry *N*,*N*-dimethylacetamide (10 mL). The solution was allowed to warm to room temperature and then heated to 55 °C for 22 h under an atmosphere of N_2. The reaction mixture was quenched with ice−water, made strongly basic with 5 M sodium hydroxide and stirred for a further 8 h. The resultant precipitate was filtered, washed with water, and dried. The crude product was purified via flash column chromatography (4:1 of dichloromethane/petroleum ether) and afforded three products.

(i) 1-(4,6-Dimethoxy-3-phenylindol-7-yl)ethanone (10). Colorless prisms (1.88 g, 65%) mp 179−181 °C (from dichloromethane/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 3.93 (s, 3H), 4.03 (s, 3H), 6.25 (s, 1H), 7.15 (d, *J* 2.6 Hz, 1H), 7.29−7.65 (m, 5H), 11.12 (br s, 1H); ^{13}C NMR ($CDCl_3$) 33.21, 55.17, 56.14, 87.20, 104.77, 110.37, 118.37, 121.71, 125.79, 127.60, 129.48, 135.77, 139.05, 159.57, 161.00, 198.63; IR 3340 (m), 1620 (m); UV 225 (18000), 250 (22100), 259 (16000), 329 (11500), 351 (9700); MS 295 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_3$ (295): C, 73.2; H, 5.8; N, 4.7. Found: C, 73.0; H, 5.9; N, 4.7.

(ii) 1-(4,6-Dimethoxy-3-phenylindol-2-yl)ethanone (11). Colorless prisms (0.58 g, 20%) mp 202−204 °C (from dichloromethane/petroleum ether). ^{1}H NMR ($CDCl_3$) δ, 2.01 (s, 3H), 3.61 (s, 3H), 3.88 (s, 3H), 6.12 (d, *J* 2.0 Hz, 1H), 6.44 (d, *J* 2.0 Hz, 1H), 7.40−7.44 (m, 5H), 9.23 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.96, 55.18, 56.60, 85.66, 93.02, 113.80, 115.00, 125.40, 127.46, 130.55, 131.09, 136.78, 137.90, 157.00, 161.03, 190.39; IR 3320 (m), 1630 (m); UV 257 (20300), 332 (19500); MS 295 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_3$ (295): C, 73.2; H, 5.8; N, 4.7. Found: C, 72.9; H, 6.0; N, 4.7.

(iii) 1-(2-Acetyl-4,6-dimethoxy-3-phenylindol-7-yl)ethanone (12). Colorless prisms (0.26 g, 8%) mp 216−218 °C (from dichloromethane/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.62 (s, 3H), 3.64 (s, 3H), 3.96 (s, 3H), 6.07 (s, 1H), 7.36 (m, 5H), 11.29 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.14, 33.07, 55.29, 56.15, 87.52, 104.35, 113.43, 124.08, 127.37, 127.45, 130.41, 131.90, 135.45, 137.88, 161.41, 163.46, 189.91, 197.64; IR 3430 (m), 1655 (m); UV 210 (21380), 241 (19750), 305 (14100), 344 (24750); MS 337 (M^+, 100). Anal. Calcd for $C_{20}H_{19}NO_4$ (337): C, 71.2; H, 5.7; N, 4.2. Found: C, 71.1; H, 5.9; N, 4.1.

General Method for Aldol Condensation of Acetylated Indoles with Aromatic Aldehydes. 1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-phenyl-2-propen-1-one (13a). Acetyl indole **10** (0.83 g, 2.82 mmol) was added to a suspension of sodium amide (0.65 g, 16.6 mmol) in anhydrous tetrahydrofuran (30 mL). The mixture was allowed to stir for 5 min, benzaldehyde (2 mL, 19.8 mmol) was added dropwise to the resulting suspension, and the mixture was stirred for a further 30min. Ice−water was then added, followed by ammonium chloride solution. The resulting yellow precipitate was filtered, washed with water and petroleum ether, dried, and recrystallized (dichloromethane/petroleum ether) to afford the indole chalcone as a yellow powder (1.0 g, 92%), mp 169−171 °C. ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 4.14 (s, 3H), 6.28 (s, 1H), 7.14 (d, *J* 2.0 Hz, 1H), 7.26−7.67 (m, 10H), 7.78 (d *J* 15.4 Hz, 1H), 8.04 (d *J* 15.9 Hz, 1H), 11.16 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.26, 56.82, 87.96, 105.48, 110.74, 118.61, 121.87, 125.83, 127.61, 128.15, 128.47, 128.76, 129.47, 129.55, 135.7, 135.99, 139.58, 140.6, 159.82, 160.77, 189.45; IR 3480 (w), 1630 (m), 1590 (s), 1570 (s); UV 228 (30000), 280 (20000), 300 (17400), 343 (11300), 397 (10500); MS 383 (M^+, 27). Anal. Calcd for $C_{25}H_{21}NO_3$ (383): C, 78.3; H, 5.5; N, 3.7. Found: C, 78.0; H, 5.8; N, 3.6.

1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-(3,4-dimethoxyphenyl)-prop-2-en-1-one (13b). This compound was prepared as described for the indole chalcone **13a** from indole **10** (0.348 g, 1.18 mmol), sodium amide (0.40 g, 11.6 mmol), and veratraldehyde (0.23 g, 1.42 mmol) in anhydrous tetrahydrofuran (20 mL), except that the suspension was heated to 50 °C for 20 min. The indole chalcone **13b** was collected and recrystallized (dichloromethane/petroleum ether) as a yellow powder (0.491 g, 94%), mp 218−220 °C. ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.07, (s, 3H), 6.98 (s, 1H), 7.18 (d, *J* 2.1 Hz, 1H), 6.89−7.61 (m, 8H), 7.74 (d, *J* 15.3 Hz, 1H), 7.93 (d, *J* 15.4 Hz, 1H), 11.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.29, 55.88, 55.99, 56.95, 88.20, 105.75, 110.38, 111.19, 116.6, 121.92, 122.27, 125.85, 126.53, 127.63, 129.09,

129.49, 139.63, 140.87, 149.12, 150.68, 159.68, 160.00, 160.59, 160.60, 193.59; IR 3360 (m), 1630 (m); UV 228 (6310), 266 (4170), 353 (4060), 396 (3380); MS 443 (M^+, 20). Anal. Calcd for $C_{27}H_{25}NO_5$ (443): C, 73.1; H, 5.7; N, 3.2. Found: C, 73.0; H, 6.0; N, 3.0.

1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-(4-methoxyphenyl)-prop-2-en-1-one (13c). This compound was prepared as described for the indole chalcone **13b** from indole **10** (0.22 g, 0.73 mmol), sodium amide (0.28 g, 7.2 mmol), and anisaldehyde (1 mL, 19.8 mmol) in anhydrous tetrahydrofuran (25 mL). The indole chalcone **13c** was collected and recrystallized (dichloromethane/petroleum ether) as a yellow powder (0.29 g, 95%), mp 204−206 °C. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 3.92 (s, 3H), 4.07 (s, 3H), 6.28 (s, 1H), 6.93 (d, *J* 8.7 Hz, 2H), 7.58 (d, *J* 8.7 Hz, 2H), 7.14 (d, *J* 2.6 Hz, 1H), 7.24−7.62 (m, 5H), 7.74 (d, *J* 15.4 Hz, 1H), 7.93 (d, *J* 15.9 Hz, 1H), 11.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.23, 55.31, 56.90, 88.12, 105.82, 110.79, 114.24, 118.53, 121.81, 125.78, 126.16, 127.58, 128.72, 129.44, 129.77, 135.75, 139.58, 140.63, 159.58, 160.58, 160.93, 189.50; IR 3320 (br m), 1620 (m); UV 235 (9930), 273 (9250), 340 (10800), 397 (8980); MS 413 (M^+, 71). Anal. Calcd for $C_{26}H_{36}NO_4$ (413): C, 75.5; H, 5.6; N, 3.4. Found: C, 75.7; H, 5.9; N, 3.3.

1-(4,6-Dimethoxy-3-phenylindol-7-yl))-3-(4-chlorophenyl)-prop-2-en-1-one (13d). This compound was prepared as described for the indole chalcone **13a** from indole **10** (0.34 g, 1.16 mmol), sodium amide (0.32 g, 8.1 mmol), and *p*-chlorobenzaldehyde (0.2 g, 1.4 mmol) in anhydrous tetrahydrofuran (30 mL), and the mixture was stirred at room temperature for 45 min. The indole chalcone **13d** was collected and recrystallized (dichloromethane/petroleum ether) as a yellow powder (0.28 g, 58%), mp 213-215 °C. ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 4.07 (s, 3H), 6.28 (s, 1H), 7.14 (d, *J* 2.6 Hz, 1H), 7.29−7.62 (m, 9H), 7.70 (d, *J* 15.9 Hz, 1H), 8.99 (d, *J* 15.4 Hz, 1H), 11.14 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.29, 56.85, 87.88, 105.6, 110.76, 118.69, 121.9, 125.89, 127.64, 128.99, 129.04, 129.28, 129.47, 134.54, 135.29, 135.64, 139.12, 139.55, 160.01, 160.82, 189.13; IR 3400 (br m), 1640 (m); UV 230 (26100), 284 (19500), 297 (18700), 307 (17700); HRMS calcd for $C_{25}H_{20}NO_3Cl$ 417.1132, found 417.1100 (^{35}Cl).

1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-phenylpenta-2,4-dien-1-one (13e). This compound was prepared as described for the indole chalcone **13a** from indole **10** (0.29 g, 0.98 mmol), sodium amide (0.10 g, 2.45 mmol) and cinnamaldehyde (0.2 mL, 2.45 mmol) in anhydrous tetrahydrofuran (30 mL), and the mixture was stirred at room temperature for 1 h. The indole chalcone **13e** after chromatography (dichloromethane) was collected and recrystallized (dichloromethane/petroleum ether) as a yellow crystalline powder (0.34 g, 85%), mp 226−228 °C. ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 4.06 (s, 3H), 6.27 (s, 1H), 7.00 (s, 1H), 7.03−7.61 (m, 14H), 11.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.32, 56.82, 88.03, 105.57, 110.80, 118.64, 121.91, 125.87, 127.09, 127.65, 128.01, 128.71, 128.79, 129.52, 132.00, 135.79, 136.69, 139.64. 139.75, 141.29, 159.77, 160.69, 189.42; IR 3310 (br m), 1610 (w); UV 235 (14000), 278 (9700), 345 (16000); HRMS calcd for $C_{27}H_{22}NO_3$ 409.1678, found 409.1621.

1-(4,6-Dimethoxy-2,3-diphenylindol-7-yl)-3-phenyl-2-propen-1-one (5).[38] This compound was prepared as described for the indole chalcone **13a** from indole **6** (0.03 g, 0.10 mmol), sodium amide (0.04 g, 1.0 mmol), and benzaldehyde (0.1 mL, 0.10 mmol) in anhydrous tetrahydrofuran (15 mL). Chalcone **5** was collected and recrystallized (dichloromethane/petroleum ether) (0.04 g, 90%), mp 195−197 °C, and shown to be identical with an authentic sample.[38]

1-(4,6-Dimethoxy-3-phenylindol-2-yl)-3-phenyl-2-propen-1-one (8). This compound was prepared as described for the indole chalcone **13a** from indole **11** (0.41 g, 1.4 mmol), sodium amide (0.22 g, 5.5 mmol), and benzaldehyde (0.5 mL, 5 mmol) in anhydrous tetrahydrofuran (20 mL). The indole chalcone **8** was collected and recrystallized (dichloromethane/petroleum ether) as a yellow powder (0.52 g, 97%) and shown to be identical with an authentic sample (see above).

1-(4,6-Dimethoxy-(7-(3-phenyl)-2-propen-1-one-3-phenylindol-2-yl))-3-phenyl-2-propen-1-one (9). This compound was prepared as described for the indole chalcone **13a** from indole **12** (0.26 g, 0.5 mmol), sodium amide (0.08 g, 2.0 mmol), and benzaldehyde (0.5 mL, 4.95 mmol) in anhydrous tetrahydrofuran (20 mL). This gave the indole chalcone **9** which was collected and recrystallized (dichloromethane/petroleum ether) as a yellow powder (0.26 g, 99%) and shown to be identical with an authentic sample (see above).

General Method for Epoxidation of Indole Chalcones. 1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-phenyl-2,3-epoxypropan-1-one (14a). Indole chalcone **13a** (0.69 g, 1.8 mmol) was dissolved in aqueous tetrahydrofuran (30 mL) to which saturated sodium hydroxide solution (10 mL) was added and the mixture allowed to stir at room temperature for 5 min. Hydrogen peroxide solution (15 mL, 30%) was added dropwise and the mixture allowed to stir for a further 6−8h. Water was added, and the resulting pale yellow precipitate was filtered, washed, and dried. After flash chromatography (dichloromethane) and recrystallization (dichloromethane/petroleum ether), the indole chalcone epoxide **14a** (0.59 g, 82%) was obtained as a pale yellow powder mp 217−219 °C. ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 3.90 (s, 3H), 4.0 (d, *J* 2.0 Hz, 1H), 4.49 (d, *J* 2.0 Hz, 1H), 6.15 (s, 1H), 7.13 (d, *J* 2.6 Hz, 1H), 7.26−7.59 (m, 10H), 10.9 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.39, 56.23, 59.06, 65.26, 87.96, 103.16, 110.63, 118.85, 122.03, 125.83, 126.05, 127.72, 128.55, 129.52, 135.48, 137.02, 138.77, 160.74, 161.57, 192.09; IR 3400 (br m), 1630 (s); UV 255 (32320), 337 (28120), 358 (1250); MS 399 (M^+, 34). Anal. Calcd for $C_{25}H_{21}NO_4$ (399): C, 75.5; H, 5.6; N, 3.5. Found: C, 75.2; H, 5.3; N, 3.5.

1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-(3,4-dimethoxyphenyl)-2,3-epoxypropen-1-one (14b). This compound was prepared as described for the indole chalcone epoxide **14a** from indole chalcone **13b** (0.12 g, 0.27 mmol), saturated sodium hydroxide solution (5 mL), and hydrogen peroxide solution (15 mL, 30%) in anhydrous tetrahydrofuran (20 mL). After flash column chromatography (dichloromethane) and recrystallization (dichloromethane/petroleum ether), the indole chalcone epoxide **14b** was obtained as a pale yellow powder (0.11 g, 86%), mp 218−220 °C. ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 6H), 3.90 (s, 3H), 3.91 (s, 3H), 3.96 (d, *J* 2.1 Hz, 1H), 4.49 (d, *J* 2.1 Hz, 1H), 6.17 (s, 1H), 6.90 (d, *J* 2.1 Hz, 1H), 6.88−7.59 (m, 9H), 10.89 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.34, 55.96, 56.31, 59.09, 59.09, 65.13, 86.99, 103.46, 108.23, 110.68, 111.03, 118.8, 121.98, 125.99, 127.64, 129.47, 135.43, 138.82, 149.26, 149.34, 160.66, 161.47, 192.09; MS 459 (M^+, 47). Anal. Calcd for $C_{26}H_{25}NO_6 \cdot {}^1/_2H_2O$ (468): C, 69.3; H, 5.5; N, 3.0. Found: C, 69.4; H, 5.5; N, 2.8.

(1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-(4-methoxyphenyl)-2,3-epoxypropan-1-one (14c). This compound was prepared as described for the indole chalcone epoxide **14a** from indole chalcone **13c** (0.249 g, 0.60 mmol), saturated sodium hydroxide solution (5 mL), and hydrogen peroxide solution (10 mL, 30%) in anhydrous tetrahydrofuran (20 mL). After flash column chromatography (dichloromethane) and recrystallization (dichloromethane/petroleum ether), the indole chalcone epoxide **14c** (0.14 g, 54%) was obtained as a pale yellow powder mp 223−225 °C. ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 3.84 (s,3H), 3.90 (s, 3H), 3.94 (d *J* 2.0 Hz, 1H), 4.51 (d *J* 2.0 Hz, 1H), 6.16 (s, 1H), 6.93 (d, *J* 8.7 Hz, 2H), 7.57 (d, *J* 8.7 Hz, 2H), 7.13 (d, *J* 2.1 Hz, 1H), 7.28−7.40 (m, 5H), 10.89 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.31, 55.32, 56.28, 58.95, 65.02, 86.99, 103.46, 110.60, 113.94, 118.77, 121.98, 125.976, 127.21, 127.64, 128.9, 129.47, 135.46, 138.72, 159.9, 160.61, 161.47, 192.28; IR 3320 (br m), 1630 (m); UV 223 (28670), 255 (29410), 335 (13250), 352 (12180); MS 429 (M^+, 27). Anal. Calcd for $C_{26}H_{23}NO_5$ (429): C, 72.7; H, 5.4; N, 3.3. Found: C, 72.5; H, 5.7; N, 3.1.

1-(4,6-Dimethoxy-3-phenylindol-7-yl)-3-(4-chlorophenyl)-2,3-epoxypropan-1-one (14d). This compound was prepared as described for the indole chalcone epoxide **14a** from indole chalcone **13d** (0.11 g, 0.27 mmol), saturated sodium hydroxide solution (5 mL), and hydrogen peroxide solution (10 mL, 30%) in anhydrous tetrahydrofuran (20 mL). After flash column chromatography (dichloromethane) and recrystallization (dichloromethane/petroleum ether), the indole chalcone epoxide **14d** was obtained as a pale yellow powder (0.08 g,

68%), mp 249−251 °C. ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 3.91 (s, 3H), 3.97 (d, *J* 2.0 Hz, 1H), 4.44 (d, *J* 2.0 Hz, 1H), 6.16 (s, 1H), 7.14 (d, *J* 2.1 Hz, 1H), 7.28−7.59 (m, 9H), 10.88 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.42, 56.31, 58.36, 65.18, 86.93, 103.38, 110.5, 112.06, 118.88, 126.07, 127.18, 127.72, 128.79, 129.50, 134.35, 135.43, 135.67, 138.74, 160.84, 161.52, 191.63; IR 3320 (br s), 1640 (s); UV 220 (14900), 255 (15100), 337 (7200), 364 (6400); MS 433.1100 (M^+, ^{35}Cl, 25). Calcd for $C_{25}H_{20}ClNO_4$ 433.1081. Anal. Calcd for $C_{25}H_{20}ClNO_4 \cdot {}^1/_2H_2O$: C, 67.8; H, 4.8; N, 3.2. Found: C, 67.4; H, 5.0; N, 3.1.

1-(4,6-Dimethoxy-2,3-diphenylindol-7-yl)-3-phenyl-2,3-epoxypropan-1-one (16). This compound was prepared as described for the indole chalcone epoxide **14a** from indole chalcone **13e** (0.026 g, 0.057 mmol), saturated sodium hydroxide solution (5 mL), and hydrogen peroxide solution (5 mL, 30%) in anhydrous tetrahydrofuran (15 mL). After flash column chromatography (dichloromethane) and recrystallization (dichloromethane/petroleum ether), the indole chalcone epoxide **16** was obtained as a pale yellow powder (0.02 g, 80%), mp 226−228 °C. ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.78 (s, 3H), 4.02 (d, *J* 2.1 Hz, 1H), 4.52 (d, *J* 2.1 Hz, 1H), 6.11 (s, 1H), 7.19−7.43 (m, 15H), 11.03 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.39, 56.20, 59.06, 65.04, 87.12, 103.26, 113.24, 114.48, 125.83, 126.26, 127.26, 127.50, 127.75, 128.50, 131.36, 132.25, 133.21, 135.54, 137.02, 137.85, 160.87, 161.41, 192.12; IR 3320 (br m), 1610 (m), 1600 (s); UV 251 (48820), 266 (50190), 312 (41390), 328 (42830), 367 (26330); MS 475 (M^+, 60). Anal. Calcd for $C_{30}H_{25}NO_4$ (475): C, 77.6; H, 5.7; N, 2.9. Found: C, 77.7; H, 5.4; N, 3.0.

1-(4,6-Dimethoxy-3-phenylindol-2-yl)-3-phenyl-2,3-epoxypropan-1-one (17). This compound was prepared as described for the indole chalcone epoxide **14a** from indole chalcone **8** (0.06 g, 0.15 mmol), saturated sodium hydroxide solution (2 mL), and hydrogen peroxide solution (5 mL, 30%) in anhydrous tetrahydrofuran (30 mL). After flash column chromatography (dichloromethane) and recrystallization (dichloromethane/petroleum ether), the indole chalcone epoxide **17** was obtained as a pale yellow powder (0.06 g, 94%), mp 195 °C. ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 3H), 3.86 (s, 3H), 3.32 (d, *J* 1.5 Hz, 1H), 3.99 (d, *J* 2.1 Hz, 1H), 6.09 (d, *J* 2.0, 1H), 6.51 (d, *J* 1.5 Hz, 1H), 6.93−7.35 (m, 10H), 9.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.12, 55.61, 59.98, 60.81, 85.59, 93.35, 113.51, 125.91, 127.15, 127.26, 128.31, 128.63, 130.03, 130.71, 134.40, 135.48, 138.88, 157.07, 161.76, 184.84; IR 3300 (br m), 1620 (s); UV 260 (23190), 346 (20030); MS 399 (M^+, 21). Anal. Calcd for $C_{25}H_{21}NO_4$ (399): C, 75.1; H, 5.6; N, 3.5. Found: C, 75.2; H, 5.3; N, 3.5.

1-(4,6-Dimethoxy-3-phenylindol-7-yl)-2-hydroxy-3-methoxy-3-phenylpropan-1-one (18). Concentrated HCl (5 drops) was added to a solution of indole epoxide **14a** (0.2 g, 0.5 mmol) in methanol (20 mL), and the solution was allowed to stir for 2h. Water (100 mL) was added, and the resulting precipitate was filtered, washed, dried, and recrystallized (dichloromethane/petroleum ether) to give the methoxy alcohol **18** (0.17 g, 80%) as a pale yellow powder, mp 217−219 °C. ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.95 (s, 3H), 4.10 (s, 3H), 4.24 (d, *J* 8.2 Hz, 1H), 4.66 (d, *J* 1.5 Hz, 1H), 5.32 (dd, *J* 2.1 Hz, 1.5 Hz, 1H), 6.3 (s, 1H), 7.16 (d *J* 2.1 Hz, 1H), 7.28−7.65 (m, 10H), 11.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.37, 56.23, 57.61, 79.35, 83.64, 87.23, 101.60, 110.95, 118.80, 122.05, 126.04, 127.43, 127.71, 128.26, 128.44, 128.52, 129.52, 135.48, 139.33, 160.64, 198.02; IR 3380 (br m), 1580 (s); UV 333 (13600), 256 (14800); MS 431 (M^+, 3). Anal. Calcd for $C_{25}H_{21}NO_4$ (431) C, 75.5; H, 5.6; N, 3.5. Found: C, 75.2; H, 5.3; N, 3.5.

General Method for Cyclization of Indole Epoxides. 5-Hydroxy-7,9-dimethoxy-1,4-diphenyl-6-oxo-6*H*-pyrrolo-[3,2,1-*ij*]quinoline (15a). Indole epoxide **14a** (0.17 g, 0.42 mmol) was dissolved in aqueous tetrahydrofuran (13 mL) to which saturated potassium hydroxide solution (3 mL) and solid potassium hydroxide (0.3 g, 5.3 mmol) were added. The reaction mixture was allowed to stir at room temperature for 4 h. Water was added, and the resulting pale yellow precipitate was filtered, washed, dried, and flash column chromatographed (97:3 of dichloromethane/methanol). After recrystallization (dichloromethane/petroleum ether), the indole flavonol **15a** was obtained as a yellow powder (0.14 g, 82%), mp 250 °C. ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H), 4.19 (s, 3H), 6.55 (s, 1H), 7.18 (s, 1H), 7.29−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 55.87, 56.79, 90.70, 103.98, 108.04, 120.23, 123.97, 125.20, 127.12, 128.01, 128.82, 129.06, 129.54, 129.69, 130.32, 133.43, 133.79, 141.34, 160.42, 162.10, 170.63; IR 3400 (br w), 3340 (w), 1610 (s); UV 244 (33300), 317 (9900), 356 (14700), 378 (11300); MS (electrospray) 398 (M^+, 100). Anal. Calcd for $C_{25}H_{19}NO_4$ (398) C, 75.6; H, 4.8; N, 3.5. Found: C, 75.2; H, 5.1; N, 3.4.

7,9-Dimethoxy-4-(3,4-dimethoxyphenyl)-5-hydroxy-1-phenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (15b). This was prepared as described for the pyrroloquinoline **15a** from indole epoxide **14b** (0.11 g, 0.24 mmol) and aqueous tetrahydrofuran (15 mL) to which were added saturated potassium hydroxide solution (3 mL) and solid potassium hydroxide (0.3 g, 5.3 mmol). After flash column chromatography (97:3 of dichloromethane/methanol) and recrystallization (dichloromethane/petroleum ether), the indole flavonol **15b** was obtained as a yellow powder (0.07 g, 60%), mp 298 °C. ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 3.96 (s, 3H), 4.02 (br s, 3H), 4.17 (br s, 3H), 6.55 (br s, 1H), 7.02−7.61 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 55.85, 56.01, 56.15, 56.77, 90.73, 103.81, 108.12, 111.25, 113.30, 120.28, 121.81, 123.19, 125.21, 127.10, 128.02, 129.04, 133.41, 133.81, 141.30, 149.10, 150.09, 160.42, 162.06, 170.58; IR 3200 (br m), 1640 (m), 1600 (s); UV 243 (10600), 332 (4600), 358 (5600), 405 (3650); MS 457 (M^+, 100). Anal. Calcd for $C_{27}H_{23}NO_6$ (457) C, 70.9; H, 5.1; N, 3.1. Found: C, 70.8; H, 5.4; N, 2.8.

7,9-Dimethoxy-5-hydroxy-4-(4-methoxyphenyl)-1-phenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (15c). This compound was prepared as described for the pyrroloquinoline **15a** from indole epoxide **14c** (0.09 g, 0.2 mmol) and aqueous tetrahydrofuran (10 mL) to which were added saturated potassium hydroxide solution (2 mL) and solid potassium hydroxide (0.2 g, 3.6 mmol). After flash column chromatography (97:3 of dichloromethane/methanol) and recrystallization (dichloromethane/petroleum ether), the indole flavonol **15c** was obtained as a yellow powder (0.05 g, 56%), mp 278−280 °C (decomp). ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 4.01 (s, 3H), 4.19 (s, 3H), 6.53 (s, 1H), 7.06 (d *J* 6.7 Hz, 2H), 7.20 (s, 1H), 7.32−7.61 (m, 5H), 7.59 (d *J* 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.37, 55.79, 56.72, 90.71, 103.73, 107.77, 114.21, 120.17, 121.46, 124.11, 127.07, 127.96, 128.99, 131.65, 133.10, 133.68, 160.34, 160.47, 162.06, 169.96; IR 2930 (w), 2820 (w), 1630 (w), 1600 (s); UV 241 (5900), 328 (2300), 357 (3000), 380 (2200); HRMS calcd for $C_{26}H_{21}NO_5$ 427.1420, found 427.1424.

4-(4-Chlorophenyl)-7,9-dimethoxy-5-hydroxy-1-phenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (15d). This compound was prepared as described for compound **15a** from indole epoxide **14d** (0.15 g, 0.34 mmol) and aqueous tetrahydrofuran (10 mL) to which were added saturated potassium hydroxide solution (2 mL) and solid potassium hydroxide (0.2 g, 3.6 mmol). After flash column chromatography (97:3 of dichloromethane/methanol) and recrystallization (dichloromethane/petroleum ether), the indole flavonol **15d** was obtained as a yellow powder (0.08 g, 54%), mp 266−268 °C. ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H), 4.17 (s, 3H), 6.54 (s, 1H), 7.14 (s, 1H), 7.27−7.61 (m, 5H), 7.50 (d *J* 8.3 Hz, 2H), 7.65 (d *J* 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.87, 56.81, 90.80, 103.83, 108.08, 119.83, 123.90, 124.25, 127.20, 128.07, 128.51, 129.05, 129.16, 131.71, 133.53, 133.67, 135.82, 141.50, 160.60, 162.21, 170.48; IR 1640 (m), 1610 (s); UV 246 (12000), 319 (3500), 357 (5500); HRMS calcd for $C_{25}H_{18}NO_4Cl$ 431.0924, found 431.0897 (Cl^{35}).

5-Acetoxy-7,9-dimethoxy-1,4-diphenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (24). Acetic anhydride (15 mL) was added to pyrroloquinoline **15a** (0.15 g, 0.63 mmol), and the mixture was allowed to stir for 4 h. Water was added, and the resulting pale yellow precipitate was filtered, washed with acetic acid and water, and then dried to yield the acetylated indole flavonol **24** (0.14 g, 86%), mp 209−211 °C, which could not be obtained analytically pure. ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.99 (s, 3H), 4.13 (s, 3H), 6.54 (s, 1H), 6.95 (s, 1H), 7.31−7.58 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.40, 55.85, 56.78, 91.53, 107.02, 108.55, 119.65, 125.29, 127.32, 128.00, 128.85, 129.11, 129.51, 130.29, 133.54, 135.92, 137.215, 138.03, 141.26, 160.14,

162.34, 169.23, 170.14); HRMS calcd for $C_{27}H_{21}NO_5Na$ 462.131179, found 462.131387.

7,9-Dimethoxy-1,4-diphenyl-4,5-dihydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (25a). Indole chalcone **13a** (0.21 g, 0.55 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) to which sodium hydride (80%) (0.04 g, 1.2 mmol) was added. The solution was brought to reflux for 1 h. After cooling, the solution was added to ice−water (50 mL) containing ammonium chloride solution (10 mL). The resulting yellow gum was extracted with dichloromethane, the extract dried ($MgSO_4$), and the solvent removed under reduced pressure to give the crude product. Preparative chromatography (97:3 of dichloromethane/methanol) afforded the title compound as a pale yellow powder (0.12 g, 56%), mp 97−99 °C. ^{1}H NMR ($CDCl_3$) δ 3.21 (d, *J* 7.2 Hz, 2H), 3.95 (s, 3H), 4.04 (s, 3H), 5.50 (t, *J* 7.2 Hz, 1H), 6.27 (s, 1H), 6.75 (s, 1H), 7.22−7.58 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 47.25, 55.42, 56.55, 59.38, 87.93, 101.81, 109.09, 119.76, 123.13, 126.10, 126.83, 127.80, 128.61, 129.12, 134.97, 139.23, 142.22, 158.66, 160.44, 188.47; IR 1660 (s); UV 218 (27600), 259 (23800), 283 (6500), 352 (8800); HRMS calcd for $C_{25}H_{21}NO_3$ 383.1521, found 383.1519.

7,9-Dimethoxy-4-(3,4-dimethoxyphenyl)-4,5-dihydro-1-phenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (25b). This was prepared as described for the indole flavanone **25a** from indole chalcone **13b** (0.25 g, 0.56 mmol) and anhydrous tetrahydrofuran (30 mL) to which was added sodium hydride (80%) (0.04 g, 1.24 mmol). The solution was refluxed for 75 min and gave the indole flavanone **25b** after preparative chromatography (97:3 of dichloromethane/methanol) as a yellow powder (0.13 g, 50%), mp 126−128 °C. ^{1}H NMR ($CDCl_3$) δ 3.06−3.26 (m, 2H), 3.81 (s, 3H), 3.87 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 5.38 (dd *J* 10.2 Hz, 5.1 Hz, 1H), 6.24 (s, 1H), 6.73 (s, 1H), 6.80−6.82 (m, 3H), 7.30−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 47.29, 55.29, 55.85, 56.41, 59.08, 87.99, 101.61, 108.97, 109.79, 111.41, 119.63, 123.08, 126.08, 127.80, 129.09, 131.24, 134.90, 142.10, 149.15, 149.32, 158.55, 160.25, 188.64; IR 1650 (s); UV 227 (28000), 259 (23000), 280 (12800), 332 (9000), 354 (9100); HRMS calcd for $C_{27}H_{25}NO_3$ 443.1733, found 443.1735.

7,9-Dimethoxy-1,4-diphenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]-quinoline (26a). Indole flavanone **25a** (0.10 g, 0.26 mmol) was dissolved in anhydrous dichloromethane (20 mL) to which was added DDQ (0.12 g, 0.56 mmol). The solution was brought to reflux for 1 h. After cooling, the solution was added to ice water (50 mL), and 20% $Na_2S_2O_5$ solution (10 mL) was added. The resulting yellow brown precipitate was extracted with dichloromethane, the dichloromethane layer dried ($MgSO_4$), and the solvent removed under reduced pressure to give the crude product as a yellow brown powder. Preparative chromatography (97:3 of dichloromethane/methanol) afforded the title compound as a pale yellow powder (0.03 g, 25%) (dichloromethane/petroleum ether), mp 288−290 °C (dec). ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 4.14 (s, 3H), 6.46 (s, 1H), 6.54 (s, 1H), 7.22 (s, 1H), 7.32−7.64 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 55.74, 56.82, 91.57, 107.52, 108.83, 117.50, 119.62, 125.34, 127.40, 128.10, 129.13, 129.22, 130.28, 132.81, 133.67, 137.99, 145.94, 159.58, 161.78, 177.87; IR 1630 (s); UV 217 (31200), 241 (29000), 270 (13400), 340 (17400), 364 (8800); HRMS calcd for $C_{25}H_{19}NO_3$ 381.1365, found 381.1366.

7,9-Dimethoxy-4-(3,4-dimethoxyphenyl)-1-phenyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (26b). This compound was prepared as described for the indole flavone **26a** from indole flavanone **25b** (0.12 g, 0.27 mmol), in anhydrous dichloromethane (25 mL), to which was added DDQ (0.14 g, 0.60 mmol) and refluxed for 1 h. Preparative chromatography (97:3 of dichloromethane/methanol) gave the indole flavone **26c** as a pale yellow powder (0.02 g, 16%) mp 324−326 °C (dec). ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 4.12 (s, 3H), 6.34 (s, 1H), 6.51 (s, 1H), 6.91−7.08 (m, 3H), 7.36−7.51 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 55.79, 55.99, 56.13, 56.77, 91.76, 107.21, 108.16, 110.59, 112.71, 120.46, 122.27, 125.48, 127.62, 127.68, 130.61, 131.72, 136.74, 141.59, 146.17, 148.48, 150.21, 158.83, 161.56, 167.55, 177.09; IR 1620 (s); UV 239 (25000), 270 (10000), 335 (13500), 366 (6900); MS 441.1892 (M^+, 100). Calcd for $C_{27}H_{23}NO_5$ 441.1576. Anal. Calcd for $C_{27}H_{23}NO_5 \cdot {}^1/_2H_2O$ (441) C, 72.0; H, 5.4; N, 3.1. Found: C, 72.1; H, 5.5; N, 3.0.

5-Benzylidene-7,9-dimethoxy-1,4-diphenyl-4,5-dihydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline (27). Indole flavanone **25a** (0.11 g, 0.29 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) under N_2. To this solution sodium hydride (80%) (0.02 g, 0.6 mmol) was added. After 5 min benzaldehyde (0.1 mL, 1.4 mmol) was added and the solution brought to reflux for 1 h. After cooling, the solution was added to ice−water (50 mL) containing ammonium chloride solution (10 mL). The resulting yellow gum was extracted with dichloromethane, the extract dried ($MgSO_4$), and the solvent removed under reduced pressure to give the crude product. Preparative chromatography (97:3 of dichloromethane/methanol) afforded the title compound as a bright yellow powder (0.09 g, 63%), mp 236−238 °C. ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 4.09 (s, 3H), 6.28 (s, 1H), 6.53 (s, 1H), 7.06 (s, 1H), 7.19−7.58 (m, 15H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.40, 56.62, 59.61, 88.39, 101.30, 108.94, 119.87, 122.74, 126.09, 126.40, 127.82, 128.26, 128.65, 128.74, 129.10, 129.30, 134.93, 135.43, 136.30, 137.72, 140.03, 140.87, 159.86, 160.64, 181.02; IR 1640 (m), 1590 (m), 1560 (s); UV 228 (13000), 282 (7900), 344 (2900); HRMS calcd for $C_{32}H_{29}NO_3$ requires 471.1834, found 471.1649.

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Supporting Information Available: Full ^{1}H NMR and ^{13}C NMR with assignments, complete listing of IR peaks, UV absorptions, and MS fragments of compounds **5**, **7**−**18**, **25a**,**b**, **26a**,**b**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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