The Synthesis and Fluorescent Properties of Analogues of the Zinc(II) Specific Fluorophore Zinquin Ester

Marc C. Kimber, Indumathy B. Mahadevan, Stephen F. Lincoln, A. David Ward,* and Edward R. T. Tiekink

Department of Chemistry, University of Adelaide, Adelaide, South Australia 5005, Australia

david.ward@adelaide.edu.au

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The synthesis and fluorescent properties in the absence and presence of zinc(II) of a range of 2-substituted derivatives of *N*-(6-methoxy-2-methyl-8-quinolyl)-4-methylbenzenesulfonamide are described. These analogues formed complexes with zinc(II) as indicated by a bathochromic shift in their UV/vis spectra. Analogues with isobutenyl and isobutyl side chains at the 2-position formed fluorescent complexes whose fluorescence was stronger than that of the 2-methyl-containing parent. These derivatives were converted, via conversion to the phenol with boron tribromide and reaction with ethyl bromoacetate, to systems with ester-containing side chains analogous to zinquin ester, a specific cellular fluorophore for zinc(II). All of these ester derivatives formed complexes with zinc(II) resulting in a bathochomic shift in their UV/vis spectra. Compounds with isobutyl, isobutenyl, and styryl side chains exhibited increased fluorescence compared to that of zinquin ester in the presence of zinc(II). The compound with the 2-isobutyl side chain was more selective in its fluorescence for zinc(II) over cadmium(II) compared to zinquin ester.

Introduction

The essential role of zinc(II) in human metabolism and the biochemical processes in which zinc(II) takes part are well documented.[1] Approximately 300 enzymes contain zinc(II), either for structural purposes or as part of a catalytic site, with the majority of this zinc(II) being tightly bound. In addition to this tightly bound zinc(II), there exists a readily exchangeable pool of less firmly bound zinc(II), termed available zinc(II), which comprises approximately 10% of the total cellular zinc(II). The latter pool is important in various processes associated with cell activation and growth. These processes include apoptosis,[2] gene expression,[3] neurotransmission,[4] signal transduction,[5] and enzyme regulation.[6] Total intracellular zinc(II) content is readily measured by standard analytical techniques, but the detection and measurement of available zinc(II) within cells has been more challenging.

In principle, this available zinc(II) could be detected by a fluorophore which complexes only with zinc(II) of the metal cations within a living cell. Fluorophores specific for other biologically prevalent cations are already available.[7] A zinc(II) fluorophore, zinquin ester **1,**[8] based on an 8-*p*-toluenesulfonamidoquinoline system,[9] has been developed by our group. Other groups have recently developed zinc(II) fluorophores based on other fluorescent systems.[10]

Zinquin ester readily traverses cell membranes and enters the cell where it is thought to be hydrolyzed by cellular esterases. The resulting acid is deprotonated at cellular pH, and the charged molecule has a decreased ability to cross the cell membrane and escape from the cell. Zinquin ester has been shown to be effective in the detection of zinc(II) in a range of mammalian cells.[11]

It is not clear whether zinquin acid binds only to the available zinc(II) within the cell or whether it can bind, at least in part, to enzyme sites that also contain zinc(II). If the binding site of the zinc(II) fluorophores were made more "sterically cluttered" then that may prevent or decrease binding of the fluorophore to enzyme-bound zinc(II) and make the fluorophore more selective for available zinc(II) within the cell.

* To whom correspondence should be addressed.

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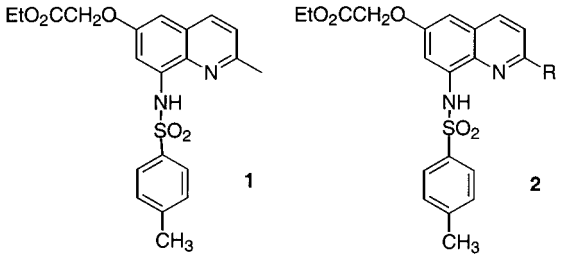
While zinquin ester is very responsive to zinc(II), detecting it at low nanomolar levels or even lower,[8b,c] it is of interest to ascertain whether an analogue of zinquin ester can be prepared that is even more sensitive. It is also of interest to establish whether the excitation wavelength of a suitable fluorophore can be changed so that, for example, the fluorophore can be used with the laser of the commonly available confocal microscopes which operate at 488 nm so that the laser light can also be used as the excitation light for the fluorophore.

The methyl group at the 2-position of zinquin ester was an important part of the design strategy for zinquin ester as it permitted us to extend this side chain, if needed, by making use of the reactive nature of this α-methyl system. This paper describes the results of our work on modifying the 2-substituent of zinquin ester, both to improve the conjugated nature of the overall molecule and hence increase the excitation wavelength of the ligand, as well as to obtain side chains with greater steric bulk than that of the methyl group which would hinder the metal binding and, hopefully, increase the selectivity of the resulting ligand.

We now report the synthesis and fluorescent properties, in the absence and presence of zinc(II), of a range of zinquin ester analogues **2** where the 2-methyl group has been replaced with larger side chains. We also report the selectivities of these new ligands in the presence of a number of metal cations, and their fluorescence compared with that of zinquin ester.

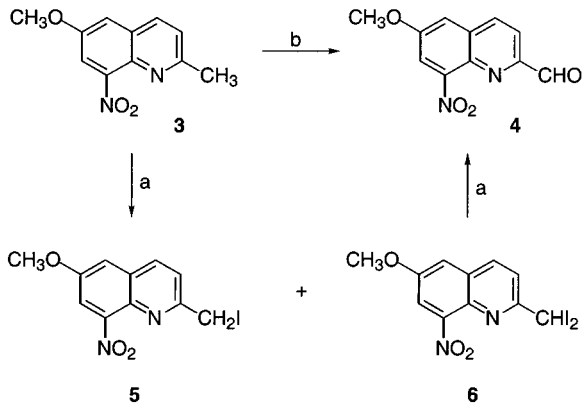


Results and Discussion

Preparation of the Ligands. The nitroquinoline **3**, prepared by the method of Mathur,[12] was oxidized to the aldehyde **4** using selenious acid.[13] The aldehyde could also be prepared, but less conveniently, from **3** by iodination to form the diiodide **6** followed by hydrolysis (Scheme 1). It was difficult to control this process, which meant that the monoiodide **5** was often a significant byproduct.

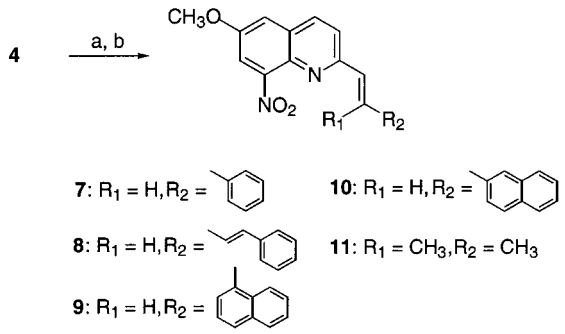
It was expected that a Wittig reaction between the aldehyde **4** and appropriate phosphonium salts would lead to the desired alkene-containing side chains. The conditions chosen for the Wittig reaction were those used by Markl and Merz,[14] since they were simple, mild, and

Scheme 1[a]



[a] Key: (a) I_2, $NaIO_3$, NaI, acetic acid; (b) H_2SeO_3, dioxane.

Scheme 2[a]



[a] Key: (a) $BrPPh_3CHR_1R_2$, CH_2Cl_2, NaOH (50%); (b) cat. TsOH, EtOH, reflux.

did not require anhydrous conditions. The styryl side chain could also be prepared by the reaction of **3** with base and benzaldehyde.

Initially, the Wittig adducts were isolated as a mixture of the cis and trans isomers, but refluxing the mixture with a catalytic amount of *p*-toluenesulfonic acid afforded the pure trans adduct (Scheme 2). The nitroquinolines **7**−**10** had coupling constants between 16.2 and 16.4 Hz for the alkene hydrogens consistent with a trans stereochemistry. Furthermore, an X-ray crystal analysis of **9** (see the Supporting Information) confirmed its trans stereochemistry. Adduct **11** contained a multiplet at δ 6.37 and two doublets at δ 2.29 and δ 1.99 indicating the presence of the isobutenyl side chain.

Selective reduction of the nitroquinolines to their corresponding amino derivatives was achieved by an iron/acetic acid method[15] without affecting the double bond. Catalytic hydrogenation of **11** reduced both functional groups to form **22**. The aminoquinolines were unstable and were tosylated under standard conditions to yield the sulfonamides **17**−**21** and **23** (Scheme 3).

Ions resulting from the loss of M − $C_7H_7SO_2$ in their mass spectra and NH absorbances at approximately 3250 cm^{-1} in their infrared spectra were seen for all of the sulfonamides. The trans stereochemistry of the starting nitro compounds was maintained throughout the sequences.

Compounds **18**−**20** showed significant fluorescence (Table 1), which rendered them unsatisfactory as ligands for the fluorescence detection of available zinc(II), whereas

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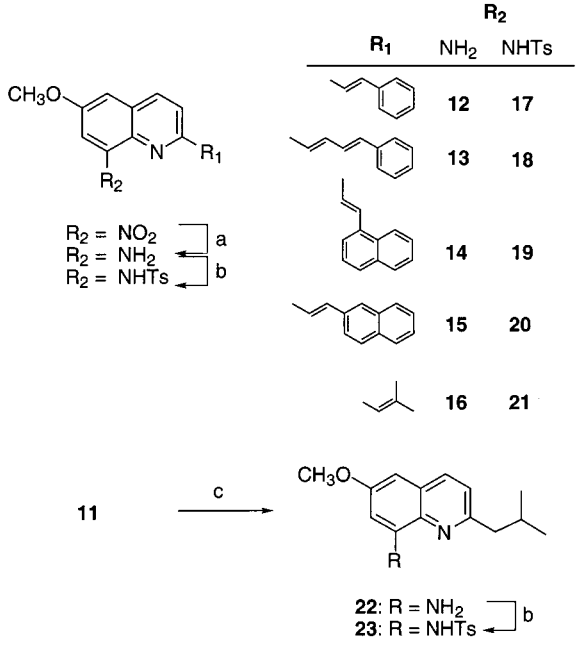
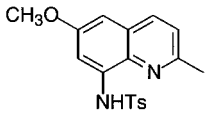
Scheme 3[a]



[a] Key: (a) Fe, AcOH, EtOH, reflux; (b) TsCl, pyridine, CH_2Cl_2; (c) H_2, Pd−C (5%), EtOH.

compounds **17**, **21**, and **23** were essentially nonfluorescent on their own but fluoresced strongly with zinc(II). The latter group were demethylated with boron tribromide, forming the corresponding hydroxy compounds **24**−**26**, which were then directly alkylated with ethyl bromoacetate to give ligands with ester groups **27**−**29** which could be saponified by esterases and therefore retained within cells (Scheme 4). This alkylation was best done using the alkylating agent in acetone with anhydrous potassium carbonate as the alternative procedure using sodium hydride and ethyl bromoacetate gave poor yields.

Physical Chemistry. Initially, the UV/vis and fluorescence measurements of these new ligands were obtained for the methoxy analogues **17**−**21** and **23** and these were then compared with the methoxy analogue of Zinquin **30**.[8a,11g]



30

All of the quinoline adducts exhibited a bathochromic shift in the presence of zinc(II). Quinolines **17**, **19**, and **20** showed similar bathochromic shifts to those seen when the methoxy analogue **30** is in the presence of zinc(II). The ligand **18** showed only a very slight bathochromic shift but the bathochromic shifts for **21** and **23** were significantly greater than that of **30**. As expected, the highest wavelength maxima for the ligands **17**−**20** were greater than that of **30** but not sufficiently so for them to absorb at 485 nm, the wavelength of the laser associated with many confocal microscopes. The fluorescence of the ligands in the absence and presence of zinc(II) was measured at their maximum absorbance values. The results are summarized in Tables 1 and 2.

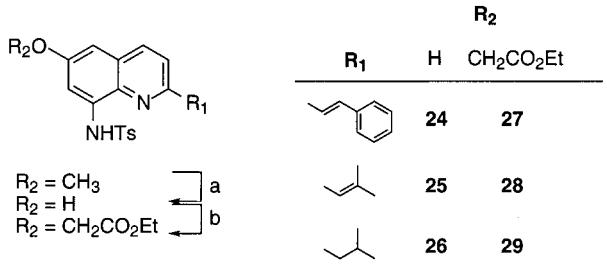
The results shown in Table 1 indicate that the incorporation of conjugated aromatic groups increases the

Table 1. Fluorescence Values Obtained for the Quinolines 17−21, 23, and 30[a−c]

quinoline	excitation λ (nm)	emission λ (nm)	fluorescence value
30	337	477	31.0 ± 1.8
17	363	410	36.0 ± 1.8
18	378	427	157.5 ± 7.6
19	369	428	196.1 ± 9.2
20	374	416	131.4 ± 6.2
21	348	488	12.1 ± 0.7
23	333	475	9.0 ± 0.5

[a] **17**−**21**, **23**, **30**: fluorescence values obtained from [L] 3.4 μM and [EDTA] 34 μM. [b] **17**−**20**: UV/vis measurements obtained from [L] 8.3 μM and [EDTA] 83 μM. [c] **21**, **23**, **30**: UV/vis measurements obtained from [L] 16.5 μM and [EDTA] 165 μM.

Scheme 4[a]



[a] Key: (a) BBr_3, CH_2Cl_2; (b) $BrCH_2CO_2Et$, base.

Table 2. Fluorescence Values Obtained for the Quinolines 17−21, 23, and 30 in the Presence of Zinc(II)[a−c]

quinoline	excitation λ (nm)	emission λ (nm)	fluorescence value
30	357	477	601.2 ± 33.2
17	377	512	319.8 ± 15.6
18	379	518	360.2 ± 17.3
19	388	515	590.2 ± 27.7
20	390	516	462.3 ± 21.7
21	382	488	872.4 ± 45.4
23	377	475	705.3 ± 36.7

[a] **17**−**21**, **23**, **30**: Fluorescence values obtained from [L] 3.4 μM and [Zn(II)] 34 μM. [b] **17**−**20**: UV/vis measurements obtained from [L] 8.3 μM and [Zn(II)] 83 μM. [c] **21**, **23**, **30**: UV/vis measurements obtained from [L] 16.5 μM and [Zn(II)] 165 μM.

fluorescence of the ligands **18**−**20**, whereas the quinolines **21** and **23** show little natural fluorescence. The fluorescence values for quinoline−zinc(II) complexes (Table 2) show that only the quinolines **21** and **23** exhibited fluorescence higher than that of the zinquin precursor **30**. The fluorescence values for the quinoline−zinc(II) complexes **17**−**21** and **23** (Table 2) are considered to arise predominantly from the complexes rather than the ligand**,** due to the high concentration of total zinc(II) in the fluorescence solutions.

The methoxy derivatives **17**, **21**, and **23** were converted to their ester derivatives, via demethylation followed by alkylation of the hydroxy compounds with ethyl bromoacetate. These three compounds were selected for conversion to their ester derivatives because both **21** and **23** showed increased fluorescence compared with **30** and **17** showed the lowest natural fluorescence out of the remaining quinolines. This yielded ligands which could be compared directly with zinquin ester in terms of fluorescence in the presence of zinc(II) and selectivity in the presence of a number of other cations.

The ligands **27**−**29** were nonfluorescent in the presence of a range of metal cations, excluding zinc(II) and

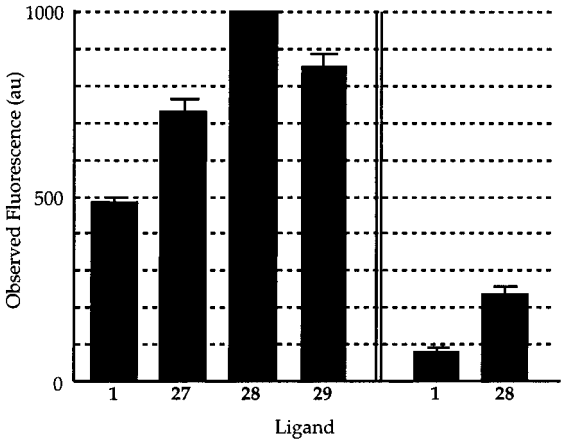


Figure 1. The observed fluorescence of ligands **27**−**29** compared to zinquin ester **1.** The fluorescence of ligand **28** and zinquin ester were also taken at a reduced slit width of 2.5 nm since the fluorescence of ligand **28** was off scale at a slit width of 5 nm. Obtained from: [L] 2 μm, [Zn(II)] 20 μm.

cadmium(II), consistent with the results that have been previously obtained for zinquin ester **1**.[11g,16,17] Of these ligands, **29** exhibited the greatest selectivity for zinc(II) over cadmium(II), showing six times the fluorescence for zinc(II) compared to cadmium(II) under the same conditions. The corresponding ratio for **27** and **28** was 3.[17] A direct fluorescence comparison of the ligands **27**−**29** with zinquin ester, **1**, in the presence of zinc(II), showed that all were more fluorescent than zinquin ester, with **28** being three times more fluorescent and **27** and **29** 1.5 and 1.75 times more fluorescent respectively (Figure 1).[18]

It must be noted that a direct comparison of the fluorescence of the ligands against zinquin ester in the presence of zinc(II) does not take into consideration the relative abundances of each species: either as ligand, ligand−zinc(II) complex, and/or di-ligand−zinc(II) complex. Preliminary studies into the relative stability of the isobutyl-, isobutenyl-, and styryl-containing ligands and zinquin ester with Zn(II) indicate that both isobutyl **29** and isobutenyl **28** containing ligands form more stable zinc(II) complexes than the corresponding zinquin ester−zinc(II) complex.[19]

Conclusion

The zinc(II) complexes of **27**−**29** are more fluorescent than the complex that zinquin ester forms with zinc(II). The isobutenyl compound **28** is three times more fluorescent than zinquin ester. The isobutyl compound **29** shows enhanced selectivity of zinc(II) compared to cadmium(II), which is the only other cation to fluoresce with these compounds. These new ligands (**27**, **28** and **29**) are significantly more sensitive for zinc(II) than zinquin ester and represent a new generation of zinc(II) fluorophores based on the 8-*p*-toluenesulfonamidoquinoline structure.

Experimental Section

General Methods. Spectroscopy. UV/vis and fluorimetric measurements were conducted using 1 cm path length silica cells thermostated at 298.2 K and a buffer solution containing 100 mM sodium perchlorate, 1 mM Na PIPES in vol/vol 75%/25% ethanol/H_2O. Zinc(II) is environmentally ubiquitous and is present as a low-level impurity even in some high-grade commercial chemicals as shown by atomic absorption measurements.[8b] Therefore, UV/vis and fluorimetric measurements of the ligands, in the absence of zinc(II), were taken in the presence of an EDTA solution.

Synthesis. ^{1}H and ^{13}C NMR spectra were obtained on a 300 MHz instrument using chloroform-*d* solutions unless otherwise indicated. Electron impact mass spectra (EIMS) were recorded at 70 eV. Accurate mass measurements were performed at the Central Science Laboratory, University of Tasmania, Tasmania, Australia. Microanalyses were performed by the Department of Chemistry, University of Otago, Dunedin, New Zealand. Flash chromatography was conducted using Merck silica gel 60 of particle size 0.040−0.063 mm. Thin Layer Chromatography (TLC) was performed on aluminum backed sheets of Merck silica gel 60F (254), which were visualized under 254 nm light. All organic extracts were dried with anhydrous analytical grade sodium sulfate. Hexane refers to the fraction of boiling range 66−68 °C. Where necessary dichloromethane was distilled from phosphorus pentoxide.

6-Methoxy-2-methyl-8-nitroquinoline (3). The title compound was prepared using a literature procedure,[12] yielding yellow-orange needle crystals (30%): mp 184−187 °C (lit.[12] mp 186−187 °C); ^{1}H NMR δ 2.72 (3H, s), 3.96 (3H, s), 7.24 (1H, d, J = 2.7 Hz), 7.34 (1H, d, J = 8.5 Hz), 7.62 (1H, d, J = 2.7 Hz), 8.00 (1H, d, J = 8.5 Hz); ^{13}C NMR δ_27.40, 58.10, 111.42, 117.60, 125.98, 130.17, 136.72, 136.93, 150.21, 157.45, 161.20; MS *m*/*z* 218 (M, 100), 188 (11), 172 (17), 160 (41).

6-Methoxy-8-nitro-2-quinolinecarbaldehyde (4). (a) To a boiling solution of selenious acid (3.56 g, 0.028 mol) in dioxane (28 mL) and water (2.8 mL) was added **3** (4.0 g, 0.018 mol) in dioxane (5 mL) and the reaction refluxed for 1 h. The hot solution was then filtered from the selenium metal and cooled and the solvent removed under reduced pressure. The residue oil was basified with saturated $NaHCO_3$ and the precipitate collected. Purification of the crude solid by flash chromatography (CH_2Cl_2) yielded the aldehyde **4** as a yellow solid (2.68 g, 63%): mp 209−211 °C (lit.[13] mp 210−212 °C); ^{1}H NMR δ 4.04 (3H, s), 7.33 (1H, d, J = 2.6 Hz), 7.77 (1H, d, J = 2.7 Hz), 8.10 (1H, d, J = 8.6 Hz), 8.26 (1H, d, J = 8.5 Hz), 10.14 (1H, s); MS *m*/*z* 232 (M, 14), 202 (23), 169 (18), 144 (45), 93 (100); HRMS calcd for $C_{11}H_8N_2O_4$ 232.0484, found 232.0489.

(b) A mixture of **3** (0.1 g, 0.047 mmol), anhydrous sodium acetate (0.018 g, 0.22 mmol), sodium iodate (0.02 g, 0.1 mmol) and iodine (0.05 g, 0.2 mol) in acetic acid (1 mL) was stirred overnight in an anhydrous atmosphere and protected from light. The dark precipitate was filtered, washed with dilute acetic acid and dried to yield a brown solid (0.14 g) which was purified by chromotography (CH_2Cl_2). Elution of the major fraction afforded a brown solid which was recystallized from CH_2Cl_2/hexane giving 2-iodomethyl-6-methoxy-8-nitro-quinoline (**5**) as brown crystals (0.075 g, 48%): mp 149−151 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.97 (3H, s), 4.64 (2H, s), 7.24 (1H, d, J = 2.5 Hz), 7.61 (1H, d, J = 8.6 Hz), 7.65 (1H, d, J = 2.5 Hz), 8.06 (1H, d, J = 8.6 Hz); EIMS *m*/*z* (relative intensity) 344 (M, 29), 343 (29), 254 (23), 218 (40), 217 (100). Anal. Calcd for $C_{11}H_9N_2O_3I$: C, 38.4; H, 2.6; N, 8.1. Found: C, 38.8; H, 2.6; N, 8.2. The crude precipitate from the iodination was treated with further iodine and sodium iodate and the product left to stand, exposed to air for 24 h. Purification by chromatography (CH_2Cl_2) gave the aldehyde **4** as a pale brown solid (0.05 g, 98%), overall yield from **3** (47%).

General Procedure for the Coupling of Phosphonium Salts to the Aldehyde 4 via the Wittig Reaction.[14] The aldehyde (1 equiv) and a phosphonium salt (1 equiv) were stirred in a biphasic solvent system consisting of CH_2Cl_2 and sodium hydroxide (50%). The reaction was stirred and checked by TLC until the reaction had finished (approximately 5 h). The aqueous layer was then extracted, the resultant organic extract dried and filtered, and solvent removed under reduced pressure. TLC indicated two products, presumably the cis and trans adducts, which upon reflux in ethanol and catalytic *p*-toluenesulfonic acid for 4−6 h were converted to one product

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(17) Data are contained in Table S2 in the Supporting Information.
(18) Data are contained in Table S3 in the Supporting Information.
(19) Kimber, M. C.; Ward, A. D.; Lincoln, S. F. Unpublished results.

(TLC). Removal of ethanol under reduced pressure followed by purification using flash chromatography (4:1 CH_2Cl_2/hexane) and crystallization (CH_2Cl_2/hexane) then yielded the required compounds. By this means the following compounds were obtained:

6-Methoxy-8-nitro-2-[(*E*)-2-phenyl-1-ethenyl]quinoline (7): yellow-green prismatic crystals (1.23 g, 93%); mp 172−174 °C; ^{1}H NMR δ 3.19 (3H, s), 7.17 (1H, d, J = 2.8 Hz), 7.25 (1H, d, J = 16.2 Hz), 7.29−7.40 (3H, m), 7.56−7.57 (2H, m), 7.60 (1H, d, J = 2.8 Hz), 7.60 (1H, d, J = 8.5 Hz), 7.67 (1H, d, J = 16.2 Hz), 8.00 (1H, d, J = 8.7 Hz); MS m/z 306 (M, 100), 305 (95), 289 (39), 69 (42); HRMS calcd for $C_{18}H_{14}N_2O_3$ 306.3196, found 306.3194.

This compound was also prepared as follows: (a) A solution of **3** (0.1 g, 0.459 mmol) in THF (2 mL) was added to a stirred suspension of NaH (80%, 70 mg) in THF (2 mL). After 15 min, benzaldehyde (10 drops) was added and the reaction mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with saturated Na_2CO_3 solution. The residue obtained after evaporation of the organic layer was purified by chromatography (CH_2Cl_2) to give **7** (0.03 g, 21%). (b) A solution of **3** (0.09 g, 0.413 mmol), benzaldehyde (0.07 g), and freshly fused zinc chloride (0.02 g) was heated in diphenyl ether at 140 °C for 15 h. The dark oil was diluted with CH_2Cl_2 and washed with Na_2CO_3 solution. The organic extract was purifed by chromatography (CH_2Cl_2) to give a mixture of **4**, diphenyl ether and benzaldehyde. (c) A solution of **3** (0.20 g, 0.917 mmol) and excess benzaldehyde was refluxed in acetic anhydride for 6 h. Dilute sodium hydroxide solution was added and the mixture extracted with CH_2Cl_2. Chromatography (CH_2Cl_2) yielded **4** (0.17 g, 60%).

6-Methoxy-8-nitro-2-[(1*E*,3*E*)-4-phenyl-1,3-butadienyl]quinoline (8): yellow plates (0.230 g, 81%); mp 166−168 °C; ^{1}H NMR δ 3.95 (3H, s), 6.83 (1H, d, J = 15.3 Hz), 6.85 (1H, d, J = 15.6 Hz), 6.95−7.06 (1H, m), 7.21 (1H, d, J = 2.7 Hz), 7.25−7.27 (1H, m), 7.31−7.37 (2H, m), 7.44−7.47 (2H, m), 7.54-(1H, d, J = 8.4 Hz), 7.54 (1H, d, J = 15.3 Hz), 7.64 (1H, d, J = 2.7 Hz), 8.01 (1H, d, J = 9.0 Hz); MS m/z 332 (M, 38), 284 (55), 226 (60), 196 (62), 97 (48), 69 (89), 43 (100). Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.3; H, 4.9; N, 8.4. Found: C, 72.2; H, 4.8; N, 8.2.

6-Methoxy-2-[(*E*)-2-(1-naphthyl)-1-ethenyl]-8-nitroquinoline (9): yellow prisms (0.240 g, 78%); mp 173.5−175 °C; ^{1}H NMR δ 3.98 (3H, s), 7.25 (1H, d, J = 2.7 Hz), 7.37 (1H, d, J = 15.6 Hz), 7.48−7.61 (3H, m), 7.69 (1H, d, J = 2.7 Hz), 7.72 (1H, d, J = 8.7 Hz), 7.84−7.90 (3H, m), 8.10 (1H, d, J = 8.7 Hz), 8.30 (1H, m), 8.60 (1H, d, J = 15.9 Hz); MS m/z 356 (M, 30), 328 (40), 308 (63), 173 (90), 69 (97), 43 (100). Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 74.2; H, 4.8; N, 7.7. Found: C, 74.0; H, 4.5; N, 7.9.

6-Methoxy-2-[(*E*)-2-(2-naphthyl)-1-ethenyl]-8-nitroquinoline (10): yellow needles (0.223 g, 73%); mp 195−197 °C; ^{1}H NMR δ 3.94 (3H, s), 7.20 (1H, d, J = 2.7 Hz), 7.39 (1H, d, J = 16.2 Hz), 7.45−7.49 (2H, m), 7.64 (1H, d, J = 2.7 Hz), 7.67 (1H, d, J = 8.7 Hz), 7.70−7.86 (4H, m), 7.83−7.93 (1H, d, J = 16.2 Hz), 7.96 (1H, m), 8.04 (1H, d, J = 8.4 Hz); MS m/z 356 (M, 80), 339 (56), 308 (100), 294 (20), 265 (60). Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 74.2; H, 4.8; N, 7.7. Found: C, 74.1; H, 4.6; N, 7.8.

2-(2-Methyl-1-propenyl)-6-methoxy-8-nitroquinoline (11): yellow needles (0.580 g, 83%); mp 143−145 °C; ^{1}H NMR: δ 1.98 (3H, d, J = 1.2 Hz), 2.29 (3H, d, J = 1.2 Hz), 3.94 (3H, s), 6.37 (1H, m), 7.19 (1H, d, J = 2.7 Hz), 7.27 (1H, d, J = 8.5 Hz), 7.62 (1H, d, J = 2.7 Hz), 7.96 (1H, d, J = 8.5 Hz); MS m/z 258 (M, 100), 228 (14), 211 (60), 168 (25). Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 65.1; H, 5.5; N, 10.9. Found: C, 64.9; H, 5.3; N, 10.9.

General Procedure for the Reduction of the Nitro Group of the Wittig Products.[15] The nitroquinoline (1 equiv), iron powder (1.5 equiv), glacial acetic acid, and ethanol were refluxed for 3.5 h under a nitrogen atmosphere. Water was added and the mixture extracted with chloroform. The organic layer was washed with saturated $NaHCO_3$ solution, dried and the solvent removed under reduced pressure. The quinolylamines quickly degraded and were used without purification in the next step. By this means the following compounds were obtained:

8-Amino-6-methoxy-2-[(*E*)-2-phenyl-1-ethenyl]quinoline (12): dark yellow solid (0.95 g, 86%); mp 143−145 °C; ^{1}H NMR δ 3.86 (3H, s), 5.05 (2H, bs), 6.45 (1H, d, J = 2.5 Hz), 6.55(1H, d, J = 2.5 Hz), 7.25−7.40 (4H, m), 7.53 (1H, d, J = 8.5 Hz), 7.57−7.62 (3H, m), 7.90 (1H, d, J = 8.5 Hz); MS m/z 276 (M, 100), 275 (35), 232 (20), 69 (60). Anal. Calcd for $C_{18}H_{16}N_2O_1$: C, 77.9; H, 5.8; N, 10.1. Found: C, 78.2; H, 5.8; N, 10.1.

8-Amino-6-methoxy-2-[(1*E*,3*E*)-4-phenyl-1,3-butadienyl]quinoline (13): dark yellow solid (0.190 g, 91%); mp 165−167 °C; ^{1}H NMR δ 3.98 (3H, s), 5.05 (2H, bs), 6.46 (1H, d, J = 2.6 Hz), 6.58 (1H, d, J = 2.6 Hz), 6.77 (12H, m), 7.53−7.88 (1H, d, J = 8.6 Hz); MS m/z 302 (M, 100), 225 (83), 182 (18), 168 (12).

8-Amino-6-methoxy-2-[(*E*)-2-(1-naphthyl)-1-ethenyl]quinoline (14): dark yellow solid (0.230 g, 93%); mp 156−158 °C; ^{1}H NMR δ 3.88 (3H, s), 5.09 (2H, bs), 6.48 (1H, d, J = 2.7 Hz), 6.58 (1H, d, J = 2.7 Hz), 7.36 (1H, d, J = 16.1 Hz), 7.48−7.58 (3H, m), 7.62 (1H, d, J = 8.5 Hz), 7.81−7.89 (3H, m), 7.93 (1H, d, J = 8.5 Hz), 8.31 (1H, m), 8.42 (1H, d, J = 16.1 Hz); MS m/z 326 (M, 32), 232 (21), 189 (16), 168 (12), 57 (100), 43 (41).

8-Amino-6-methoxy-2-[(*E*)-2-(2-naphthyl)-1-ethenyl]quinoline (15): yellow needles (0.187 g, 99%); mp 158−160 °C; ^{1}H NMR δ 3.87 (3H, s), 5.08 (2H, bs), 6.46 (1H, d, J = 2.5 Hz), 6.57 (1H, d, J = 2.6 Hz), 7.40−7.48 (3H, m), 7.58 (1H, d, J = 8.5 Hz), 7.77 (1H, d, J = 16.2 Hz), 7.81−7.86 (4H, m), 7.92 (1H, d, J = 8.5 Hz), 7.94 (1H, m); MS m/z 326 (M, 10), 149 (20), 43 (100).

8-Amino-6-methoxy-2-(2-methyl-1-propenyl)quinoline (16): yellow/green oil (0.163 g, 83%); ^{1}H NMR δ 1.99 (3H, d, J = 1.0 Hz), 2.24 (3H, d, J = 1.0 Hz), 3.84 (3H, s), 4.95 (2H, bs), 6.41−6.43 (2H, m), 6.55 (1H, d, J = 2.4 Hz), 7.18 (1H, d, J = 8.5 Hz), 7.84 (1H, d, J = 8.5 Hz); MS m/z 228 (M, 100), 213 (10), 169 (12).

8-Amino-2-isobutyl-6-methoxyquinoline (22). 2-Isobutenyl-6-methoxy-8-nitro-quinoline **21** (0.400 g, 1.739 mmol) was dissolved in ethanol (50 mL) and stirred with Pd−C(5%) (20 mg) under an atmosphere of hydrogen for 16 h. After filtration of the solution through Celite, followed by removal of the solvent under reduced pressure, the amine **22** was obtained, as a yellow/green oil (0.345 g, 86%), which quickly degraded and was used without purification in the next step: ^{1}H NMR δ 0.98−0.95 (6H, m), 2.21 (1H, m), 2.78−2.74 (2H, m), 3.85 (3H, s), 5.01 (2H, bs), 6.44 (1H, d, J = 2.4 Hz), 6.55 (1H, d, J = 2.4 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.82 (1H, d, J = 8.4 Hz); MS m/z 230 (M, 58), 215 (20), 188 (100), 173 (15), 144 (10).

General Procedure for the Tosylation of the Amines. The quinolylamine (1 equiv) was stirred with tosyl chloride (1 equiv) in CH_2Cl_2 and pyridine overnight. The organic layer was washed with HCl (1M) followed by a solution of saturated $NaHCO_3$. The organic extracts were dried, the solvent was removed under reduced pressure, and the crude solid was chromatographed (CH_2Cl_2 followed by elution of the required compound with ethyl acetate) and then recrystallized (CH_2Cl_2/hexane).

4-Methyl-*N*-(6-methoxy-2-[(*E*)-2-phenyl-1-ethenyl]-8-quinolyl)benzenesulfonamide (17): pale orange crystals (1.05 g, 71%); mp 185.5−187.5 °C; ^{1}H NMR δ_2.28 (3H, s), 3.85 (3H, s), 6.67 (1H, d, J = 2.5 Hz), 7.17 (2H, d, J = 8.3 Hz), 7.29 (1H, d, J = 16.4 Hz), 7.30−7.44 (4H, m), 7.55 (1H, d, J = 16.4 Hz), 7.58 (1H, d, J = 8.5 Hz), 7.61−7.64 (2H, m), 7.83 (2H, d, J = 8.3 Hz), 7.90 (1H, d, J = 8.6 Hz), 9.24 (1H, bs); MS m/z 430 (M, 30), 275 (M − $C_7H_7SO_2$, 25), 91 (33), 69 (100), 41 (83). Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 69.8; H, 5.2; N, 6.5. Found: C, 69.8; H, 5.0; N, 6.4.

4-Methyl-*N*-(6-methoxy-2-[(1*E*,3*E*)-4-phenyl-1,3-butadienyl]-8-quinolyl)benzenesulfonamide (18): yellow crystals (0.208 g, 89%); mp 213-215 °C; ^{1}H NMR δ_2.92 (3H, s), 3.84 (3H, s), 6.65 (1H, d, J = 2.4 Hz), 6.83 (1H, d, J = 15.9 Hz), 6.88 (1H, d, J = 16.2 Hz), 6.99−7.10 (1H, m), 7.17 (2H, d, J = 8.1 Hz), 7.46 (1H, d, J = 8.4 Hz), 7.44 (1H, d, J = 16 Hz),

7.25−7.51 (6H, m), 7.83 (2H, d, J = 8.1 Hz), 7.86 (1H, d, J = 8.4 Hz), 9.21 (1H, bs); MS m/z 457 (M, 10), 302 (M − $C_7H_7SO_2$, 30); HRMS calcd for $C_{27}H_{24}N_2O_3S$ 456.1508, found m/z 456.1518.

4-Methyl-*N*-(6-methoxy-2-[(*E*)-2-(1-naphthy)-1-ethenyl]-8-quinolyl)benzenesulfonamide (19): yellow prisms (0.267 g, 93%); mp 166−168 °C; ^{1}H NMR δ_2.29 (3H, s), 3.87 (3H, s), 6.69 (1H, d, J = 2.4 Hz), 7.17 (2H, d, J = 8.1 Hz), 7.36 (1H, d, J = 16.2 Hz), 7.46 (1H, d, J = 2.4 Hz), 7.51−7.62 (3H, m), 7.68 (1H, d, J = 8.7 Hz), 7.83−7.91 (4H, m), 7.94 (1H, d, J = 8.7 Hz), 8.26 (2H, d, J = 8.1 Hz), 8.33 (1H, d, J = 16.2 Hz), 9.26 (1H, bs); MS m/z 481 (M, 10), 480 (20), 325 (M−$C_7H_7SO_2$, 40), 43 (100); HRMS calcd for $C_{29}H_{24}N_2O_3S$ 480.1508, found m/z 480.1508. Anal. Calcd for $C_{29}H_{24}N_2O_3S$: C, 72.5; H, 5.0; N, 5.8. Found: C, 72.5; H, 5.2; N, 5.9.

4-Methyl-*N*-(6-methoxy-2-[(*E*)-2-(2-naphthy)-1-ethenyl]-8-quinolyl)benzenesulfonamide (20): yellow prisms (0.204 g, 85%); mp 185−187 °C; ^{1}H NMR δ_2.29 (3H, s), 3.85 (3H, s), 6.67 (1H, d, J = 2.5 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.39 (1H, d, J = 16.2 Hz), 7.43, 1H, d, J = 2.5 Hz), 7.47−7.51 (2H, m), 7.61 (1H, d, J = 8.5 Hz), 7.73 (1H, d, J = 16.2 Hz), 7.82−7.87 (6H, m), 7.91, 1H, d, J = 8.5 Hz), 7.99 (1H, m), 9.28 (1H, bs); MS m/z 481 (M, 10), 447 (99), 325 (M − $C_7H_7SO_2$, 20), 168 (26), 84 (100); HRMS calcd for $C_{29}H_{24}N_2O_3S$ 480.1508, found m/z 480.1515.

4-Methyl-*N*-(6-methoxy-2-(2-methyl-1-propenyl)-8-quinolyl)benzenesulfonamide (21): white prisms (0.244 g, 91%); mp 158−160 °C; ^{1}H NMR δ 2.00 (3H, m), 2.19 (3H, m), 2.27 (3H, s), 3.83 (3H, s), 6.36 (1H, m), 6.63 (1H, d, J = 2.4 Hz), 7.13 (1H, d, J = 8.3 Hz), 7.20 (1H, d, J = 8.4 Hz), 7.24 (1H, d, J = 2.4 Hz), 7.77 (1H, d, J = 8.3 Hz), 7.82 (1H, d, J = 8.4 Hz), 9.13 (1H, bs); MS m/z 382 (M, 50), 227 (M − $C_7H_7SO_2$, 100). Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 66.0; H, 5.8; N, 7.3. Found: C, 65.7; H, 5.8; N, 7.2.

4-Methyl-*N*-(2-isobutyl-6-methoxy-8-quinolyl)benzenesulfonamide (23): white needles (0.490 g, 85%); mp 154−156 °C; ^{1}H NMR δ 0.91 (6H, m), 2.13 (1H, m), 2.27 (3H, s), 2.72 (2H, m), 3.84 (3H, s), 6.66 (1H, d, J = 2.7 Hz), 7.12 (1H, d, J = 8.3 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.43 (1H. d. J = 2.7 Hz), 7.76 (2H, d, J = 8.3 Hz), 7.82 (1H, d, J = 8.4 Hz), 9.25 (1H, bs); MS m/z 384 (M, 33), 229 (M−$C_7H_7SO_2$, 30), 187 (88), 69 (100). Anal. Calcd for $C_{21}H_{24}N_2O_3S$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.9; H, 6.5; N, 7.3.

General Procedure for the Demethylation of the Methoxy Compounds. To a solution of boron tribromide (2.5 equiv) in dry CH_2Cl_2 under N_2 was added dropwise a solution of the sulfonamide (1 equiv) in dry CH_2Cl_2. The reaction mixture was refluxed for 4 h then stirred for 16 h. Water was added cautiously to the mixture, which was basified with a solution of saturated $NaHCO_3$ and the aqueous layer extracted with CH_2Cl_2. The organic extracts were combined and dried, and the solvent was removed under vacuum. The crude solid was then used directly in the next step.

4-Methyl-*N*-(6-hydroxy-2-[(*E*)-2-phenyl-1-ethenyl]-8-quinolyl)benzenesulfonamide (24): orange crystalline solid (0.85 g, 84%); mp 242−245 °C; ^{1}H NMR δ_1.93 (3H, s), 6.36 (1H, d, J = 2.4 Hz), 6.83 (2H, d, J = 8.3 Hz), 6.90 (1H, d, J = 16.5 Hz), 7.06 (1H, d, J = 2.4 Hz), 6.98−7.07 (3H, m), 7.16−7.29 (5H, m), 7.44 (2H, d, J = 8.3 Hz), 7.49 (1H, d, J = 8.7 Hz), 9.31 (1H, bs); MS m/z 416 (M, 100), 261 (M − $C_7H_7SO_2$, 90), 91 (55), 77 (30).

4-Methyl-*N*-[6-hydroxy-2-(2-methyl-1-propenyl)-8-quinolyl]benzenesulfonamide (25): yellow oil (0.22 g, 98%); ^{1}H NMR δ 1.98 (3H, s), 2.15 (3H, s), 2.16 (3H, s), 6.32 (1H, m), 6.72 (1H, m), 7.03 (2H, d, J = 8.4 Hz), 7.11 (1H, d, J = 8.5 Hz), 7.49 (1H, m), 7.68 (1H, d, J = 8.5 Hz), 7.74 (2H, d, J = 8.4 Hz), 9.28 (1H, bs); MS m/z 368 (M, 29), 213 (M − $C_7H_7SO_2$, 100), 198 (20), 91 (32).

4-Methyl-*N*-(2-isobutyl-6-hydroxy-8-quinolyl)benzenesulfonamide (26): orange needles (0.37 g, 87%); mp 147−149 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (6H, m), 2.10 (1H, m), 2.27 (3H, s), 2.71 (2H, d, J = 7.2 Hz), 6.71 (1H, d, J = 2.5 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.15 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 2.5 Hz), 7.75 (2H, d, J = 8.5 Hz), 7.79 (1H, d, J = 8.4 Hz), 9.25 (1H, bs); MS m/z 372 (M, 33), 217 (M − $C_7H_7SO_2$, 100), 91 (63).

Ethyl 2-(2-[(*E*)-2-Phenyl-1-ethenyl]-6-quinolyloxy-8-*p*-toluenesulfonamido)acetate (27). To a suspension of sodium hydride (0.097 g, 2.22 mmol) in DMF (10 mL) at 0 °C was added a solution of the phenol **24** (0.840 g, 2.01 mmol) in DMF (20 mL) and the reaction mixture stirred for 20 min. under an N_2 atmosphere. Ethyl bromoacetate (0.225 mL, 2.01 mmol) was then added and the reaction mixture allowed to warm to room temperature and then stirred overnight. The DMF was then removed under vacuum, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with a solution of saturated $NaHCO_3$ (100 mL). Purfication by flash chromatography (CH_2Cl_2) followed by recrystallization (CH_2Cl_2/hexane) yielded the ester **27** as white needles (0.30 g, 30%): mp 178−179.5 °C; IR (KBr) υ 3325, 1760, 1610, 1600 cm^{-1}; ^{1}H NMR δ 1.29 (3H, t, J = 7.2 Hz), 2.29 (3H, s), 4.27 (2H, q, J = 7.2 Hz), 4.67 (2H, s), 6.62 (1H, d, J = 2.7 Hz), 7.17 (2H, d, J = 8.4 Hz), 7.29 (1H, d, J = 16.2 Hz), 7.33−7.44 (3H, m), 7.51 (1H, d, J = 2.7 Hz), 7.55 (1H, d, J = 16.2 Hz), 7.58 (1H, d, J = 8.6 Hz), 7.63 (2H, m), 7.83 (2H, d, J = 8.4 Hz), 7.88 (1H, d, J = 8.6 Hz), 9.25 (1H, bs); MS m/z 502 (M, 100), 347 (M − $C_7H_7SO_2$, 45), 319 (15), 232 (25), 91 (24). Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C, 66.9; H, 5.2; N, 5.6. Found: C, 66.8; H, 5.4; N, 5.7.

Ethyl 2-[2-(2-Methyl-1-propenyl)-6-quinolyloxy-8-*p*-toluenesulfonamido]acetate (28). The phenol **25** (0.215 g, 0.583 mmol), ethyl bromoacetate (0.065 mL, 0.59 mmol), and potassium carbonate (0.081 g, 0.59 mmol) were refluxed in dry acetone (15 mL) for 4 h under N_2. The solvent was then removed under vacuum, the residue was dissolved in CH_2Cl_2 and washed with a solution of saturated $NaHCO_3$. The crude product was purified by flash chromatography and then recrystallized from CH_2Cl_2/hexane yielding the ester **28** as white needles (0.182 g, 67%): mp 149−151 °C; ^{1}H NMR δ 1.29 (3H, t, J = 6.9 Hz), 2.01 (3H, d, J = 1.4 Hz), 2.19 (3H, d, J = 1.4 Hz), 2.29 (3H, s), 4.27 (2H, q, J = 6.9 Hz), 4.66 (2H, s), 6.37 (1H, t, J = 1.4 Hz), 6.61 (1H, d, J = 2.6 Hz), 7.16 (2H, d, J = 8.3 Hz), 7.22 (1H, d, J = 8.6 Hz), 7.51 (1H, d, J = 2.6 Hz), 7.78 (2H, d, J = 8.3 Hz), 7.82 (1H, d, J = 8.6 Hz), 9.15 (1H, bs); MS m/z 454 (M, 52), 299 (M − $C_7H_7SO_2$, 100), 184 (20), 91 (21). Anal. Calcd for $C_{24}H_{26}N_2O_5S$: C, 63.4; H, 5.8; N, 6.2. Found: C, 63.1; H, 5.8; N, 6.3.

Ethyl 2-(2-Isobutyl-6-quinolyloxy-8-*p*-toluenesulfonamido)acetate (29). The phenol **26** (0.334 g, 0.90 mmol) was refluxed with ethyl bromoacetate (0.100 mL, 0.90 mmol) and potassium carbonate (0.124 g, 0.90 mol) in dry acetone (15 mL) for 4 h under N_2. The solvent was then removed under vacuum, and the crude solid was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. Purification by flash chromatography followed by recystallisation from CH_2Cl_2/hexane yielded the ester **29** as a white solid (0.375 g, 90%): mp 146.5−148.5 °C; ^{1}H NMR δ 0.90 (6H, m), 1.29 (3H, t, J = 7.2 Hz), 2.11 (1H, m), 2.28 (3H, s), 2.72 (2H, d, J = 6.9 Hz), 4.27 (2H, q, J = 7.2 Hz), 4.66 (2H, s), 6.63 (1H, d, J = 2.6 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.17 (1H, d, J = 8.3 Hz), 7.54 (1H, d, J = 2.6 Hz), 7.77 (2H, d, J = 8.5 Hz), 7.82 (1H, d, J = 8.3 Hz), 9.26 (1H, bs); IR (KBr) υ 3260, 1760, 1630, 1610, 1590 cm^{-1}; MS m/z 456 (M, 77), 414 (20), 301 (M−$C_7H_7SO_2$, 32), 259 (100), 155 (19), 91 (55). Anal. Calcd for $C_{24}H_{28}N_2O_5S$: C, 63.1; H, 6.2; N, 6.2. Found: C, 63.0; H, 6.3; N, 6.2.

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Supporting Information Available: X-ray data for **9**; tabulated fluorescence values (Table S2) for **17**−**21** and **23** with a number of metal cations; tabulated fluorescence values (Table S3) of **1** and **27**−**29** in the absence and presence of zinc(II), and ^{1}H NMR spectra of **7**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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