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Heteroaryl Cross-Coupling as an Entry toward the Synthesis of Lavendamycin Analogues: A Model Study

Guido Verniest,[‡,§] Xingpo Wang,*[,†,¶] Norbert De Kimpe,[‡] and Albert Padwa*[,†]

[†]*Department of Chemistry, Emory University, Atlanta, Georgia 30322,* [¶]*School of Chemistry and Chemical Engineering, Shandong University, Shandong 250100, People's Republic of China, and* [‡]*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Gent, Belgium.* [§]*Postdoctoral Fellow of the Research Foundation Flanders (FWO-Vlaanderen, Belgium) at Emory University.*

chemap@emory.edu; xpw6@sdu.edu.cn

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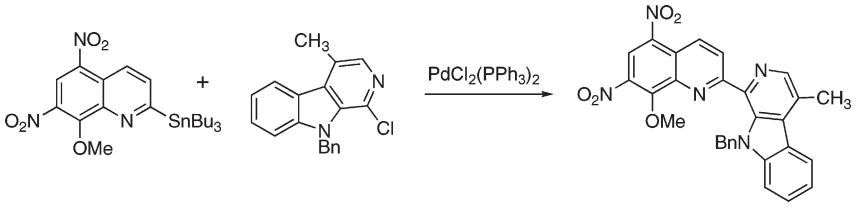

ABC analogues of the antitumor antibiotic lavendamycin, which contain the key metal chelation site and redox-active quinone unit essential for biological activity, were prepared *via* the palladium(0)-catalyzed cross-coupling reaction of various 2-haloheteroaromatics with 2-stannylated pyridines and quinolines. Using the Stille reaction, 2-bromo substituted quinolines and 1-bromoisoquinolines were found to undergo efficient coupling with 2-pyridinylstannanes to provide unsymmetrical heterobiaryl derivatives. While the Stille reaction using the reverse coupling partners (*i.e.*, 2-quinolinylstannanes and haloheteroaromatics) had not received much attention in the literature, we found that this alternative coupling reaction efficiently provided several new heterobiaryl derivatives. The gold-catalyzed intramolecular cycloisomerization of *N*-(prop-2-ynyl)-1*H*-indole-2-carboxamide smoothly afforded a β-carbolinone derivative that was subsequently used for a Pd(0)-catalyzed cross-coupling directed toward the synthesis of lavendamycin analogues.

Introduction

Lavendamycin (**1**), a highly substituted and functionalized 7-aminoquinoline-5,8-dione, was isolated and characterized in 1981 by Doyle from the fermentation broths of *Streptomyces lavendulae*.[1] In structure as well as in bioassays, lavendamycin (**1**) is closely related to streptonigrin (**2**) (Figure 1), another potent antitumor antibiotic.[2] Both of these compounds have been shown to possess cytotoxic properties and exhibit significant activity against topoisomerases.[3] Consequently, these target molecules have been the focus of much synthetic effort since their initial structural identification. The first total synthesis of lavendamycin methyl ester was reported by Kende and Ebetino in 1984.[4] They accomplished the synthesis of **1** through a Bischler−Napieralski condensation of a substituted quinaldic acid with β-methyltryptophan methyl ester followed by cyclization and functionalization of the A ring. The subsequent Boger group's synthesis of **1** was based on a Friedlander condensation of a functionalized amino aldehyde with a β-carboline to build the B-ring.[5] Still another approach involves a modified Knoevenagel−Stobbe pyridine formation and further D-ring construction by a thermolytic nitrene insertion.[6] Several

(1) (a) Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.-H.; Moews, A. E. *Tetrahedron Lett*. **1981**, *22*, 4595. (b) Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot*. **1982**, *35*, 259.

(2) (a) Bringmann, G.; Reichert, Y.; Kane, V. V. *Tetrahedron* **2004**, *60*, 3539. (b) Rao, K. V.; Cullen, W. P. *Antibiot. Annu*. **1959**, 950. (c) Rao, K. V.; Biemann, K.; Woodward, R. B. *J. Am. Chem. Soc*. **1963**, *85*, 2532. (d) Chiu, Y. Y. H.; Lipscomb, W. N. *J. Am. Chem. Soc*. **1975**, *97*, 2525.

(3) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem*. **1987**, *30*, 1918.

(4) (a) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett*. **1984**, *25*, 923. (b) Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E. *Heterocycles* **1984**, *21*, 91.

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(6) Ciufolini, M. A.; Bishop, M. J. *J. Chem. Soc., Chem. Commun*. **1993**, 1463.

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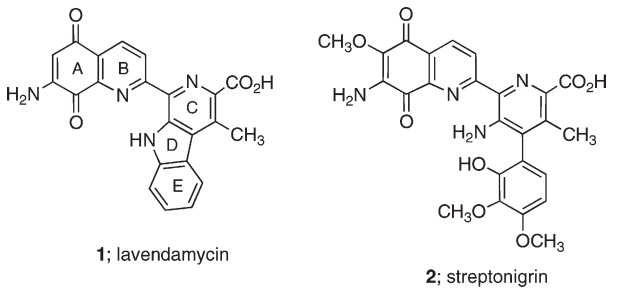
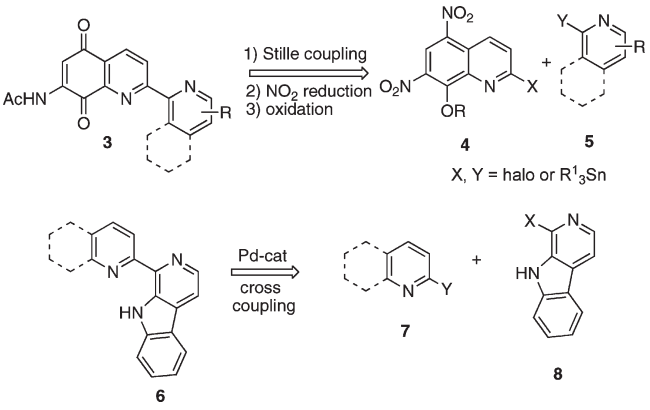


FIGURE 1. Some potent antitumor antibiotics.

additional syntheses of this compound and of ester derivatives were also carried out.[7] As a consequence of the promising bioactivity of lavendamycin (**1**) and analogues, the synthesis and structure−activity relationship (SAR) studies of this class of compounds remain an active area of research.[8] A limitation to exploiting the biological properties of lavendamycin is its toxicity that may be partly due to the presence of the quinone moiety in the A-ring. In this respect, several new lavendamycin derivatives have recently been prepared that show potent antitumor and anti-HIV reverse transcriptase activities, with low general cellular toxicity.[9] It was also observed that among the lavendamycins tested, the presence of an acetyl group on the C_7-amino group enhanced the selectivity in cell toxicity.[9] The fascinating structural features coupled with the interesting biological activity of lavendamycin led us to undertake an eventual synthesis of this complex molecule as well as its analogues, with a view of finding activity better than that of the parent compound. A retrosynthesis of the much simpler *N*-acetyl analogue of lavendamycin (*i.e.*, **3**) revealed to us that this skeletal framework could be obtained from a Pd(0)-catalyzed cross-coupling reaction of two key intermediates, namely, a 2-halo- (or 2-stannyl)-5,7-dinitro-8-alkoxy substituted quinoline **4** with a 2-pyridinylstannane (or halide) **5** (Scheme 1). Using this model system, our intention was to first reduce the nitro groups of the cross-coupled product and then oxidize the resulting compound to give the required quinoline-5,8-dione ring system **3**. In addition, we hoped to use our recently developed methodology of synthesizing 1-halo-β-carbolines of type **8** *via* the Au(III)-catalyzed cycloisomerization of *N*-propargyl indole-2-carboxamides[10] to provide a new entry

SCHEME 1



toward other lavendamycin analogues (*i.e.*, **6**) employing a related cross-coupling reaction with 2-substituted pyridines **7**.

Results and Discussion

The 2,2′-bipyridine unit is a key structural feature found in some important natural products that show antibiotic and cytotoxic activities.[11] Nowadays these substituted bipyridines are frequently prepared by transition-metal-catalyzed cross-coupling reactions.[12−15] The palladium(0)-catalyzed cross-coupling of aryl halides to form unsymmetrical biaryls corresponds to one of the most useful reactions in synthetic organic chemistry.[16] Several of the more common methods for performing this coupling are the Stille (organostannane),[17] Suzuki−Miyaura

(7) (a) Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261. (b) Hibino, S.; Okazaki, M.; Sato, K.; Morita, I.; Ichikawa, M. *Heterocycles* **1983**, *20*, 1957. (c) Rao, A. V. R.; Chavan, S. P. *Tetrahedron* **1986**, *42*, 5065. (d) Behforouz, M.; Haddad, J.; Cai, W.; Arnold, M. B.; Mohammadi, F.; Sousa, A. C.; Horn, M. A. *J. Org. Chem.* **1996**, *61*, 6552. (e) Hassani, M.; Cai, W.; Koelsch, K. H.; Holley, D. C.; Rose, A. S.; Olang, F.; Lineswala, J. P.; Holloway, W. G.; Gerdes, J. M.; Behforouz, M.; Beall, H. D. *J. Med. Chem.* **2008**, *51*, 3104. (f) Nourry, A.; Legoupy, S.; Huet, F. *Tetrahedron Lett.* **2007**, *48*, 6014. (g) Chan, B. K.; Ciufolini, M. A. *J. Org. Chem.* **2007**, *72*, 8489. (h) Seradj, H.; Cai, W.; Erasga, N. O.; Chenault, D. V.; Knuckles, K. A.; Ragains, J. R.; Behforouz, M. *Org. Lett.* **2004**, *6*, 473. (i) Fryatt, T.; Petterson, H. I.; Gardipee, W. T.; Bray, K. C.; Green, S. J.; Slawin, A. M. Z.; Beall, H. D.; Moody, C. J. *Bioorg. Med. Chem.* **2004**, *12*, 1667. (j) McElroy, W. T.; DeShong, P. *Org. Lett.* **2003**, *5*, 4779.

(8) Nourry, A.; Legoupy, S.; Huet, F. *Tetrahedron* **2008**, *64*, 2241.

(9) (a) Behforouz, M.; Cai, W.; Mahammadi, F.; Stocksdale, M. G.; Gu, Z.; Ahmadian, M.; Baty, D. E.; Etling, M. R.; Al-Anzi, C. H.; Swiftney, T. M.; Tanzer, L. R.; Merriman, R. L.; Behforouz, N. C. *Bioorg. Med. Chem.* **2007**, *15*, 495. (b) Behforouz, M.; Cai, W.; Stocksdale, M. G.; Lucas, J. S.; Jung, J. Y.; Briere, D.; Wang, A.; Katen, K. S.; Behforouz, N. C. *J. Med. Chem.* **2003**, *46*, 5773.

(10) (a) England, D.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631. (b) For a related alkynyl indole cycloisomerization, see: Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.

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(13) Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, L. J.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2777.

(14) Gronowitz, S.; Björk, P.; Malm, J.; Hörnfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127.

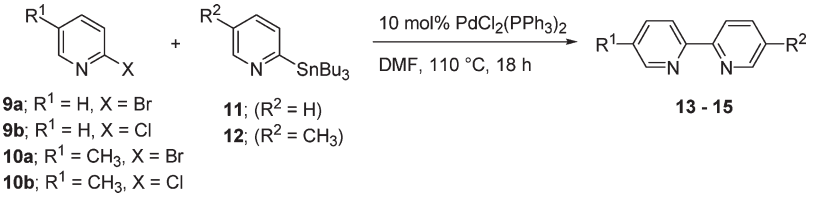
(15) For a recent review on 2,2′-bipyridine synthesis, see: (a) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, 235. (b) Hapke, M.; Brandt, L.; Lützen, A. *Chem. Soc. Rev.* **2008**, *37*, 2782.

(16) (a) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Schroter, S.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (e) Diederich, P.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (f) Negishi, E. *Handbook of Organopalladium Chemisty for Organic Synthesis*; John Wiley and Sons: New York, 2002; Vol. 1. (g) Fugami, K.; Kosugi, M. *Top. Curr. Chem.* **2002**, *219*, 87. (h) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (i) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(17) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (c) Yamamoto, Y.; Azuma, Y.; Mitoh, H. *Synthesis* **1986**, *7*, 564. (d) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Rivière, E; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169. (e) Schwab, P. F. H.; Fleischer, F.; Michl, J. *J. Org. Chem.* **2002**, *67*, 443.

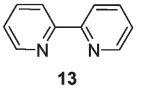
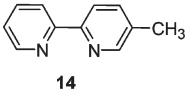
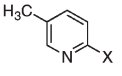
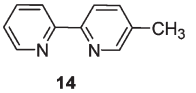
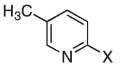
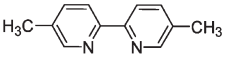
(18) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11 and references therein. (c) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6787. (d) Lipshutz, B. H.; Ghoral, S. *Aldrichimica Acta* **2008**, *41*, 59. (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (f) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047. (g) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (h) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (i) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (j) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (k) *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, 2004. (l) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201. (m) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

TABLE 1. Stille Cross-Coupling Reaction of 2-Halopyridines



9a; R^1 = H, X = Br
9b; R^1 = H, X = Cl
10a; R^1 = CH_3, X = Br
10b; R^1 = CH_3, X = Cl

11; (R^2 = H)
12; (R^2 = CH_3)

Entry	2-Halo-pyridines **9a,b** or **10a,b**	2-Stannyl-pyridines **11** or **12**	Bipyridines **13-15**	Yield
1	 **9a** or **9b**	**11**	 **13**	78% (from **9a**, X = Br) 56% (from **9b**, X = Cl)
2	 **9a** or **9b**	**12**	 **14**	66% (from **9a**, X = Br) 44% (from **9b**, X = Cl)
3	 **10a** or **10b**	**11**	 **14**	59% (from **10a**, X = Br) 41% (from **10b**, X = Cl)
4	 **10a** or **10b**	**12**	 **15**	61% (from **10a**, X = Br) 35% (from **10b**, X = Cl)

(organoboron),[18] and Hiyama (organosilicon)[19] reactions. The more established Stille reaction has benefited from high yields, wide functional group tolerances, and high turnovers of the palladium catalyst.[17] Furthermore, a diverse array of functionalized organostannanes are readily available by a number of different reaction types.[17] While some information is available concerning the Stille cross-coupling of stannylated pyridines and 2-halogenated quinolines,[20] little is known about the related coupling using the reverse partners (*i.e.*, 2-stannylated quinolines with 2-substituted pyridines).[21] With the intention of gaining additional insight into the scope of the metal-catalyzed cross-coupling of suitably substituted quinolyl and pyridinyl precursors, a number of ABC analogues of lavendamycin were synthesized using different stannylated heteroaromatics and halogenated pyridines, isoquinolines, and β-carbolines in order to evaluate the efficiency of the coupling reaction.[22]

The first coupling experiments were conducted with various 2-halogenated pyridines (*i.e.*, **9a**−**10b**)[23] and 2-tributylstannylpyridines **11** and **12** in DMF at 110 °C using $PdCl_2(PPh_3)_2$ as the catalyst. The results clearly demonstrated that higher yields of the coupled bipyridines **13**,[17c] **14**,[24] and **15**[25] were obtained when 2-bromopyridines were used as substrates as compared to the corresponding 2-chloropyridines (Table 1).

The strategy to assemble the ABC ring system of lavendamycin outlined in Scheme 1 was next applied to the synthesis of the simpler analogue **19**. In addition to providing the functional groups present in the A-ring of lavendamycin, it was anticipated that the presence of a methoxy group in precursor **18** would direct the dinitration to afford the required quinoline **19** which would be further utilized to eventually give the desired *para*-quinone A-ring found in compound **3**.

The synthesis of the starting 2-bromoquinoline **18** is depicted in Scheme 2. Commercially available 2,8-dihydroxyquinoline (**16**) was treated with acetic anhydride followed by a subsequent reaction with $POBr_3$ in refluxing $CHCl_3$ to give 8-acetoxy-2-bromoquinoline (**17**) in 67% overall yield. Hydrolysis of the ester moiety in **17** followed by reaction with methyl iodide gave the corresponding methyl ether **18**, which was readily converted to 2-bromo-8-methoxy-5,7-dinitroquinoline (**19**)

(19) (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Stang, P. J., Ed.; Wiley-VCH Verlag GmbH: Weinheim, 1998; pp 421−452. (b) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (c) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58.

(20) (a) Godard, A.; Fourquez, J. M.; Tamion, R.; Marsais, F.; Quéguiner, G. *Synlett* **1994**, 235. (b) Godard, A.; Rocca, P.; Pomel, V.; Dumont, T. L.; Rovera, J. C.; Thaburet, J. F.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1996**, *9*, 2195. (c) Kimber, M.; Anderberg, P. I.; Harding, M. M. *Tetrahedron* **2000**, *56*, 3575.

(21) (a) Godard, A.; Rovera, J.-C.; Marsais, F.; Plé, N.; Quéguiner, G. *Tetrahedron* **1992**, *48*, 4123. (b) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 3325.

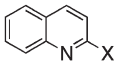
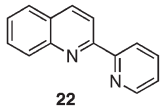
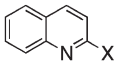
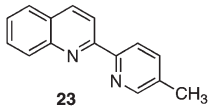
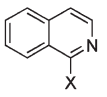
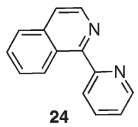
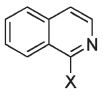
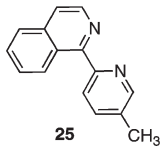
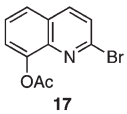
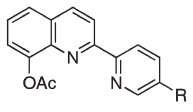
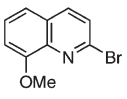
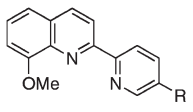
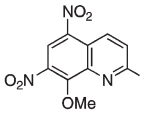
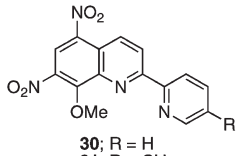
(22) For a somewhat related approach, see: Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron Lett.* **1993**, *34*, 2937.

(23) For the preparation of 2-halopyridines **10a,b**, see: (a) Zhang, H.; Tse, M. K.; Chan, K. S. *Synth. Commun.* **2001**, *31*, 1129. (b) Nicolaou, K. C.; Scarpelli, R.; Bollbuck, B.; Werschkun, B.; Pereira, M. M. A.; Wartmann, M.; Altmann, K.-H.; Zaharevitz, D.; Gussio, R.; Giannakakou, P. *Chem. Biol.* **2000**, *7*, 593. (c) Bedel, S.; Ulrich, G.; Picard, C.; Tisnes, P. *Synthesis* **2002**, *11*, 1564.

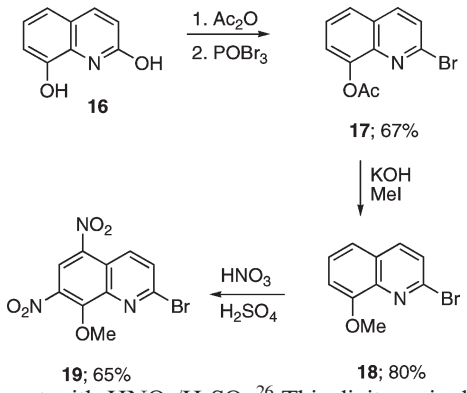
(24) (a) Schubert, U. S.; Eschbaumer, C.; Heller, M. *Org. Lett.* **2000**, *2*, 3373. (b) Potts, K. T.; Winslow, P. A. *J. Org. Chem.* **1985**, *50*, 5405.

(25) Schubert, U. S.; Eschbaumer, C.; Hochswimmer, G. *Synthesis* **1999**, *5*, 779.

TABLE 2. Stille Reaction of Halogenated Quinolines and Isoquinolines with 2-Stannylpyridines using $PdCl_2(PPh_3)_2$

Entry	R^1-X	R^2-$SnBu_3$ / solvent	R^1-R^2 (**22-31**)	Yield
1	 **20a**; X = Br **20b**; X = Cl	**11** / DMF	 **22**	71% (from **20a**) 51% (from **20b**)
2	 **20a**; X = Br **20b**; X = Cl	**12** / DMF	 **23**	59% (from **20a**) 46% (from **20b**)
3	 **21a**; X = Br **21b**; X = Cl	**11** / DMF	 **24**	41% (from **21a**) 38% (from **21b**)
4	 **21a**; X = Br **21b**; X = Cl	**12** / DMF	 **25**	44% (from **21a**) 35% (from **21b**)
5	 **17**	**11** or **12** / DMF	 **26**; R = H **27**; R = CH_3	57% (from **11**; R = H) 49% (from **12**; R = CH_3)
6	 **18**	**11** or **12** / DMF	 **28**; R = H **29**; R = CH_3	78% (from **11**; R = H) 82% (from **12**; R = CH_3)
7	 **19**	**11** or **12** / toluene	 **30**; R = H **31**; R = CH_3	61% (from **11**; R = H) 60% (from **12**; R = CH_3)

SCHEME 2



by treatment with HNO_3/H_2SO_4.[26] This dinitroquinoline derivative can be easily obtained on multigram scale and serves as a suitable precursor for the 7-amino-5,8-dione moiety of lavendamycin (*vide infra*). We found that the cross-coupling reaction of 2-haloquinolines **20**, 1-haloisoquinolines **21**, and the substituted 2-bromoquinolines **17**−**19** proceeded in a manner similar to that observed in the pyridine series (see Table 1). Thus, the palladium(0)-catalyzed coupling between these halogenated quinolines and 2-stannylated pyridines **11** and **12** using the Stille procedure produced the expected heterobiaryls **22**−**31** in good yield.[27−29] The results are summarized in Table 2 and show that

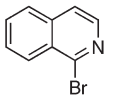
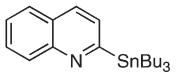
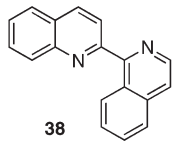
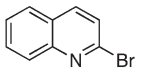
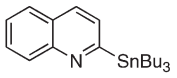
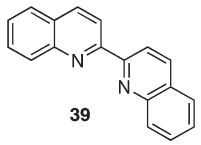
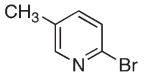
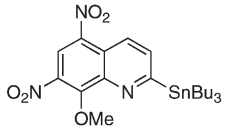
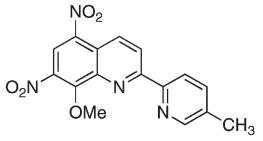
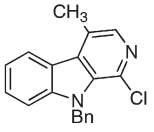
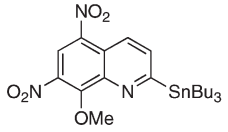
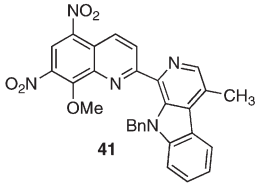
(26) (a) Sigouin, O.; Beauchamp, A. L. *Can. J. Chem.* **2005**, *83*, 460. (b) Gershan, H.; Clarke, D. D. *Monatsh. Chem.* **1991**, *122*, 935. (c) Petitjean, A.; Kyritsakas, N.; Lehn, J.-M. *Chem.—Eur. J.* **2005**, *11*, 6818. (d) Holzapfel, C. W.; Ferreira, A. C.; Marais, W. *J. Chem. Res.* **2002**, 218.

(27) Martinez, R.; Ramon, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988.

(28) Haginiwa, J.; Higuchi, Y.; Kawashima, T.; Goto, T. *Yakugaku Zasshi* **1975**, *95*, 204.

(29) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

TABLE 3. Stille Reaction of 2-Stannylquinolines with Halogenated Heteroaromatics

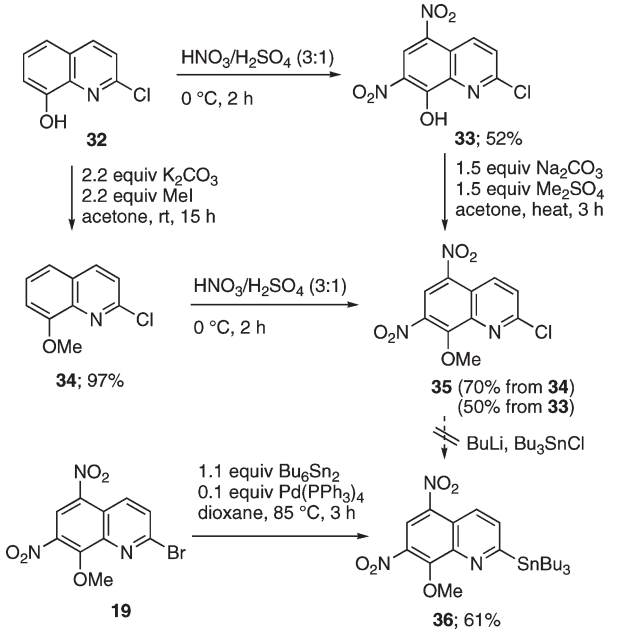
Entry	R^1-X	R^2-$SnBu_3$ / solvent	Product R^1-R^2	Yield
1	 **21a**	 **37** / DMF	 **38**	49%
2	 **20a**	 **37** / DMF	 **39**	68%
3	 **10a**	 **36** / toluene	 **31**	63%
4	 **40**	 **36** / toluene	 **41**	63%

$PdCl_2(PPh_3)_2$ is an efficient catalyst for these haloquinoline coupling reactions. Yields refer to isolated materials, and reactions were carried out with 10 mol % of catalyst in DMF or toluene for 6 h at 105 °C.

Experiments were also undertaken to compare the efficiency of the cross-coupling reaction using 2-stannylated quinolines (*i.e.*, **36** and **37**; see Table 3) as the reaction partners. Our first attempt to prepare 2-tributylstannylquinoline **36** is outlined in Scheme 3. 2-Chloro-8-methoxy-5,7-dinitroquinoline (**35**) was synthesized by the dinitration of 2-chloro-8-hydroxyquinoline (**32**)[26] to give **33** followed by O-methylation using dimethyl sulfate. An alternative and somewhat higher-yielding approach to **35** involved carrying out the O-methylation in the first step to first furnish 2-chloro-8-methoxyquinoline (**34**) in nearly quantitative yield, and this was followed by a subsequent dinitration reaction to give **35**. Unfortunately, the lithiodechlorination of **35** using *n*-BuLi and then reacting the resultant aromatic anion with *n*-Bu_3SnCl failed to give any of the desired stannylated product. It was found, however, that the coupling of the corresponding 2-bromoquinoline **19** with $Bu_3SnSnBu_3$ and $PdCl_2(PPh_3)_2$ in dioxane at 85 °C for 3 h produced the desired 2-stannylquinoline **36** in 61% yield after silica gel chromatography.

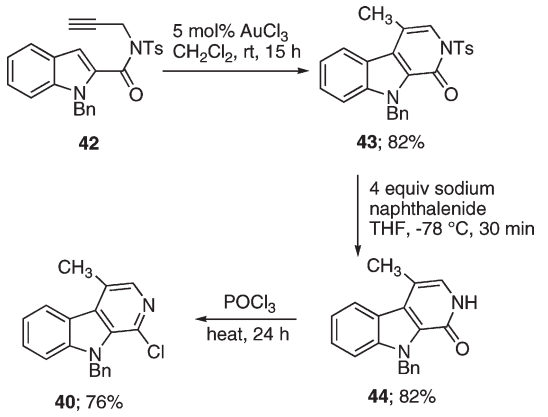
A Stille reaction using the above 2-stannylated quinoline **36** as well as the simpler stannane **37** derived from commercially available 2-bromoquinoline was carried out with the halogenated pyridine **10a**, quinoline **20a**, isoquinoline **21a**, and β-carboline **40** as the coupling partners. While the reactivity of heteroaryl chlorides such as 1-chloroisoquinoline **21b** (X = Cl) in Stille couplings is well-established, higher yields may be obtained under Negishi conditions.[30] We found that the coupling of stannane **37** with 1-chloroisoquinoline (**21b**) under either standard Pd(0)[17] or Ni(0) catalysis[30] gave poor overall yields of the coupled product **38**. However, 1-bromoisoquinoline (**21a**) underwent smooth coupling with stannane **37** to furnish the biaryl product **38** in 49% yield. Similarly, 2-bromoquinoline **20a** was also coupled with stannane **37** to

SCHEME 3



(30) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

SCHEME 4

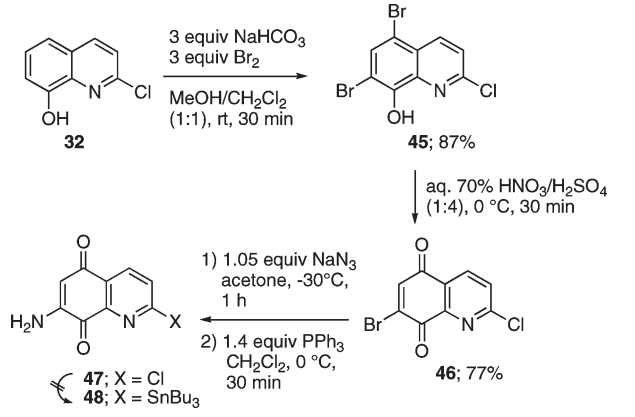


afford the expected biaryl coupled product **39** in 68% yield (Table 3). We then extended this procedure to the coupling reaction of 2-stannylated dinitroquinoline **36**, which represents a more advanced compound for the synthesis of lavendamycin analogues. It was found that the Stille cross-coupling of **36** with 2-bromopyridine **10a** gave the expected 2-pyridylquinoline **31** in 63% yield. Likewise, the reaction of **36** with 1-chloro-β-carboline **40** proceeded smoothly to give the coupled product **41** in 63% yield (Table 3). 1-Chloro-β-carboline **40** was easily accessible in bulk and in 51% overall yield in three steps from *N*-propargyl-*N*-tosyl-1-benzylindole-2-carboxamide **42** using our recently reported method to access β-carbolines *via* a gold(III)-catalyzed cycloisomerization.[10] Thus, the reaction of **42** with a catalytic quantity of $AuCl_3$ afforded 2-tosyl-β-carbolinone **43**, which was subjected to *N*-detosylation with sodium naphthalenide, and the resulting amide **44** was subsequently treated with $POCl_3$ to give **40** in 62% yield from **43** (Scheme 4).

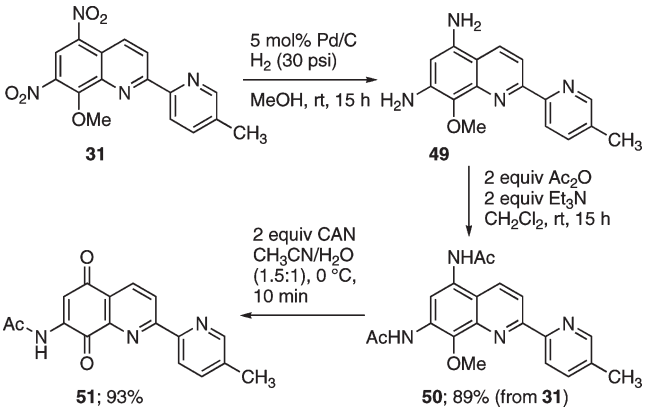
To determine whether 7-aminoquinolinediones could be used directly as coupling partners for the synthesis of lavendamycin analogues, 7-amino-2-chloroquinolinedione **47** was prepared from 2-chloro-8-hydroxyquinoline (**32**) (Scheme 5). This was accomplished by treating quinoline **32** with bromine to give 5,7-dibromo-2-chloro-8-hydroxyquinoline **45**. Further reaction of quinoline **45** with nitric/sulfuric acid furnished 7-bromo-2-chloroquinolin-5,8-dione **46** in 77% yield. Treatment of **46** with sodium azide afforded 7-azido-2-chloroquinoline-5,8-dione. Unfortunately, the reduction of the azido group to the corresponding amino functionality produced only **47** in low yield (*ca.* 25%). Furthermore, all attempts to convert quinolinedione **47** into the corresponding stannyl derivative **48** failed, and consequently we abandoned this particular approach toward the synthesis of lavendamycin and its analogues.

An alternate strategy for an eventual synthesis of lavendamycin was also evaluated using 2-(pyridin-2-yl)quinoline **31** as a potential precursor (Scheme 6). Hydrogenation of **31** over Pd/C followed by subsequent acylation of **49** with acetic anhydride gave the diacetamido substituted quinoline **50** in 89% yield. Oxidation of **50** with cerium ammonium nitrate (CAN) furnished 7-acetamido-5,8-dione **51** in 93% yield. Thus, this sequence of reactions allows for the construction of the ABC skeleton of lavendamycin by using a Stille cross-coupling at a much earlier stage of the synthesis.

SCHEME 5



SCHEME 6



In conclusion, 2-bromo substituted quinolines efficiently couple with 2-pyridinylstannanes to provide unsymmetrical heterobiaryl derivatives. The overall approach shows a good convergence and is currently being extended to the synthesis of lavendamycin and analogues starting from functionalized quinolines and β-carboline building blocks.

Experimental Section

2-Bromo-8-methoxy-5,7-dinitroquinoline (19). A mixture containing 2.7 g (10 mmol) of 8-acetoxy-2-bromoquinoline (**17**),[26c] 2.0 g (30 mmol) of KOH, and 25 mL of ethanol was stirred for 1 h at ambient temperature. After removal of the solvent under reduced pressure, water was added to form a clear solution which was brought to pH 7 with hydrochloric acid. The mixture was extracted with chloroform, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 2.15 g (88%) of 2-bromo-8-quinolinol as a white solid: mp 81−82 °C (lit.[26a] mp 81−82 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, 1H, J = 7.6 and 1.2 Hz), 7.32 (dd, 1H, J = 8.4 and 1.2 Hz), 7.68 (s, 1H), 7.52 (m, 2H) and 7.98 (d, 1H, J = 8.8 Hz).

To a solution of 2.2 g (10 mmol) of the above 2-bromo-8-quinolinol in 50 mL of acetone was added 4.1 g (30 mmol) of K_2CO_3 at room temperature, and the heterogeneous solution was rapidly stirred under a dry nitrogen atmosphere. A 2.0 mL (30 mmol) sample of MeI was added over 5 min, and the solution was stirred overnight at room temperature. The solvent was removed under reduced pressure, and then 75 mL of water was added. The mixture was extracted with CH_2Cl_2, dried over

$MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give 2.33 g (97%) of 2-bromo-8-methoxyquinoline (**18**)[26d] as a white solid: mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.14 (dd, 1H, J = 7.9 and 1.0 Hz), 7.31 (dd, 1H, J = 7.9 and 1.0 Hz), 7.48 (m, 2H), and 7.91 (d, 1H, J = 8.8 Hz).

To 12 mL of a stirred solution of $HNO_3-H_2SO_4$ (3:1 v/v) was added 2.38 g (10 mmol) of 2-bromo-8-methoxyquinoline (**18**) in small portions. The mixture was allowed to stir at 0 °C for 2 h and then poured into 150 mL of ice . The bright yellow solid that formed was filtered, washed with ice−water, and then dried overnight to give 2.47 g (65%) of 2-bromo-8-methoxy-5,7-dinitroquinoline (**19**) as a light yellow solid: mp 97−98 °C; IR (neat) 3106, 2955, 1573, 1526, 1341, and 843 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (s, 3H), 7.88 (d, 1H, J = 9.2 Hz), 8.78 (s, 1H) and 9.00 (d, 1H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.5, 121.6, 123.9, 131.3, 135.1, 138.7, 140.0, 142.8, 143.6 and 154.9. Anal. Calcd for $C_{10}H_6BrN_3O_5$: C, 36.70; H, 1.85; N, 12.85. Found: C, 36.80; H, 1.76; N, 12.70.

1-(5-Methylpyridin-2-yl)isoquinoline (25). To a solution of 1-bromoisoquinoline (**21a**) (0.1 g, 0.5 mmol) in 1 mL of dry degassed DMF were added 2-tri-*n*-butylstannyl-5-methylpyridine (**12**) (0.19 g, 0.5 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 110 °C for 18 h. After cooling to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layers were washed with water and brine and then dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.048 g (44%) of the titled compound **25** as a pale yellow oil: IR (neat) 3049, 2922, 1553, 1484, 1134, and 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.58 (m, 1H), 7.69 (m, 3H), 7.90 (t, 2H, J = 8.4 Hz) and 8.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 121.0, 124.7, 126.7, 126.8, 127.5, 127.8, 130.0, 132.9, 137.1, 137.4, 141.9, 149.0, 155.6, and 157.7. HRMS Calcd for [($C_{15}H_{12}N_2$) + H^+]: 221.1079. Found: 221.1075.

Preparation of 2-(Pyridin-2-yl)quinolin-8-yl Acetate (26). To a solution of 2-bromo-8-acetoxyquinoline (**17**) (0.13 g, 0.5 mmol) in 1 mL of dry degassed DMF were added 2-tri-*n*-butylstannyl-pyridine (**11**) (0.18 g, 0.5 mmol) and dichlorobis(triphenyl-phosphine)palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 105 °C for 6 h and cooled to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.076 g (57%) of the titled compound **26** as a light yellow solid: mp 145−147 °C; IR (neat) 2923, 2852, 1767, 1597, 1204, and 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 7.39 (m, 1H), 7.47 (m, 1H), 7.54 (m, 1H), 7.74 (m, 1H), 7.87 (m, 1H), 8.32 (d, 1H, J = 8.8 Hz), 8.56 (d, 1H, J = 8.6 Hz), 8.65 (d, 1H, J = 8.8 Hz) and 8.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 119.8, 121.6, 121.9, 124.4, 125.9, 126.6, 129.7, 137.0, 137.1, 140.7, 148.0, 149.3, 156.1, 156.2, 170.0. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.63; H, 4.61; N, 10.44.

Preparation of 2-(5-Methylpyridin-2-yl)quinolin-8-yl Acetate (27). To a solution of 2-bromo-8-acetoxyquinoline (**17**) (0.13 g, 0.5 mmol) in 1 mL of dry degassed DMF were added 2-tri-*n*-butylstannyl-5-methylpyridine (**12**) (0.19 g, 0.5 mmol), and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 105 °C for 6 h and cooled to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.068 g (49%) of the titled compound **27** as a light yellow solid: mp 157−159 °C; IR (neat) 2921, 2852, 1767, 1597, 1196, and 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.57 (s, 3H), 7.39 (m, 1H), 7.50 (m, 1H), 7.66 (m, 1H), 7.74 (m, 1H), 8.28 (d, 1H, J = 8.8 Hz), 8.44 (d, 1H, J = 8.6 Hz), 8.53 (s, 1H) and 8.59 (d, 1H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 21.0, 119.4, 121.2, 121.3, 125.7, 126.2, 129.4, 134.0, 136.8, 137.4, 140.4, 147.7, 149.5, 153.5, 156.0, 169.7. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.35; H, 5.07; N, 10.07. Found: C, 73.36; H, 5.23; N, 9.98.

Preparation of 8-(Methoxy-2-pyridin-2-yl)quinoline (28). To a solution of 2-bromo-8-methoxyquinoline (**18**) (0.12 g, 0.5 mmol) in 1 mL of dry degassed DMF were added 2-tri-*n*-butylstannyl-pyridine (**11**) (0.18 g, 0.5 mmol) and dichlorobis(triphenyl-phosphine)palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 105 °C for 6 h and cooled to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.092 g (78%) of the titled compound **28** as a white solid: mp 74−76 °C; IR (neat) 2925, 2853, 1589, 1458, 1260, and 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 3H), 7.08 (d, 1H, J = 7.2 Hz), 7.34 (m, 1H), 7.45 (m, 2H), 7.86 (m, 1H), 8.27 (d, 1H, J = 8.4 Hz), 8.60 (d, 1H, J = 8.8 Hz) and 8.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.3, 108.1, 119.6, 120.0, 122.2, 124.1, 127.1, 129.5, 136.9, 137.0, 142.6, 149.1, 155.2, 155.7, and 156.4. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12; N, 11.86. Found: C, 76.28; H, 5.14; N, 11.76

Preparation of 8-Methoxy-2-(5-methylpyridin-2-yl)quinoline (29). To a solution of 2-bromo-8-methoxyquinoline (**18**) (0.12 g, 0.5 mmol) in 1 mL of dry degassed DMF were added 2-tri-*n*-butylstannyl-5-methylpyridine (**12**) (0.19 g, 0.5 mmol) and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 105 °C for 6 h and cooled to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give the titled compound **29** (82%) as a light yellow solid: mp 94−95 °C; IR (neat) 2924, 2853, 1599, 1462, 1259, and 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.11 (s, 3H), 7.07 (dd, 1H, J = 7.2 and 1.2 Hz), 7.43 (m, 2H), 7.66 (d, 1H, J = 7.2 Hz), 8.24 (d, 1H, J = 8.4 Hz) and 8.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 56.4, 108.1, 119.6, 120.0, 121.9, 127.0, 129.5, 134.0, 137.0, 137.7, 140.0, 149.7, 154.0, 155.5, and 155.7. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20. Found: C, 76.62; H, 5.66; N, 11.06.

Preparation of 8-(Methoxy-5,7-dinitro-2-pyridin-2-yl)quinoline (30). To a solution of 2-bromo-8-methoxy-5,7-dinitroquinoline (**19**) (0.16 g, 0.5 mmol) in 1 mL of dry degassed toluene were added 2-tri-*n*-butylstannylpyridine (**11**) (0.18 g, 0.5 mmol) and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 100 °C for 6 h and cooled to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.099 g (61%) of the titled compound **30** as a light yellow solid: mp 182−184 °C; IR (neat) 2921, 2851, 1568, 1529, 968, and 853 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 3H), 7.50 (m, 1H), 7.96 (m, 1H), 8.65 (d, 1H, J = 7.6 Hz), 8.81 (d, 1H, J = 4.4 Hz), 8.82 (s, 1H), 9.02 (d, 1H, J = 9.2 Hz), 9.29 (d, 1H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.7,

120.9, 122.2, 124.3, 124.9, 125.6, 128.6, 128.8, 132.1, 132.3, 132.4, 133.9, 137.5, 149.9 and 154.4. Anal. Calcd for $C_{15}H_{10}N_4O_5$: C, 55.20; H, 3.09; N, 17.18. Found: C, 55.19; H, 3.14; N, 17.20.

8-Methoxy-2-(5-methylpyridin-2-yl)-5,7-dinitroquinoline (31). To a solution of 2-bromo-8-methoxy-5,7-dinitroquinoline (**19**) (0.16 g, 0.5 mmol) in 1 mL of dry degassed toluene were added 2-tri-*n*-butylstannyl-5-methyl-pyridine (**14**) (0.19 g, 0.5 mmol) and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere, and the mixture was heated at 100 °C for 6 h. After cooling to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and then dried over Na_2SO_4. The organic extract was filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give the titled compound **31** in 60% as a light yellow solid: mp 197−199 °C; IR (neat) 2921, 2851, 1557, 1531, 1321, and 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 4.66 (s, 3H), 7.73 (d, 1H, J = 8.4 Hz), 8.52 (d, 1H, J = 8.0 Hz), 8.60 (s, 1H), 8.79 (s, 1H), 8.96 (d, 1H, J = 9.2 Hz) and 9.25 (d, 1H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 65.6, 120.7, 121.7, 124.1, 128.6, 128.8, 132.1, 132.3, 132.4, 133.7, 135.8, 137.9, 150.3, 151.8 and 157.5. Anal. Calcd for $C_{16}H_{12}N_4O_5$: C, 56.46; H, 3.56; N, 16.47. Found: C, 56.38; H, 3.64; N, 16.38.

8-Methoxy-2-(5-methylpyridin-2-yl)-5,7-dinitroquinoline (**31**) could also be prepared by the coupling of 2-tri-*n*-butylstannyl-8-methoxy-5,7-dinitroquinoline (**36**) with 2-bromo-5-methylpyridine (**10a**). To a solution of 2-bromo-8-methoxy-5,7-dinitroquinoline (**19**) (0.16 g, 0.5 mmol) in 5 mL of dry degassed dioxane were added bis(tributyltin) (0.32 g, 0.55 mmol) and tetrakis-(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) under an argon atmosphere, and the mixture was heated at 85 °C for 3 h. After cooling to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and then dried over Na_2SO_4. The organic extract was filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.17 g (61%) of 2-tri-*n*-butylstannyl-8-methoxy-5,7-dinitroquinoline (**36**) as a light yellow oil, IR (neat) 2956, 2925, 1557, 1528, 1336, and 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 9H, J = 7.2 Hz), 1.25 (m, 6H), 1.35 (m, 6H), 1.62 (m, 6H), 4.62 (s, 3H), 7.87 (d, 1H, J = 8.4 Hz), 8.77 (s, 1H) and 8.90 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 13.8, 27.7, 29.2, 65.4, 120.4, 124.0, 128.1, 133.2, 139.3, 143.0, 156.0, 181.2. HRMS Calcd for $[C_{22}H_{33}N_3O_5Sn + H^+]$: 540.1520. Found: 540.1518.

2-Tri-*n*-butylstannyl-8-methoxy-5,7-dinitroquinoline (**36**) (0.27 g, 0.5 mmol) and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) were added to a solution of 2-bromo-5-methylpyridine (**10a**) (0.086 g, 0.5 mmol) in 5 mL dry degassed toluene under an argon atmosphere, and the mixture was heated at 100 °C for 6 h. After cooling to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and then dried over Na_2SO_4. The organic extract was filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.16 g (63%) of the titled compound **31**.

Preparation of 2-Chloro-8-methoxy-5,7-dinitroquinoline (35). To a solution of 2.0 g (11.1 mmol) of 2-chloro-8-hydroxyquinoline (**32**) in 50 mL of acetone was added 3.5 g (25.4 mmol) of K_2CO_3 at room temperature, and the heterogeneous solution was stirred under a dry nitrogen atmosphere for 30 min. To this mixture was added 1.7 mL (25.4 mmol) of MeI over a 5 min period, and the solution was stirred overnight at room temperature. The solvent was removed under reduced pressure, 75 mL of water was added to the residue, and the mixture was extracted with CH_2Cl_2. After drying over $MgSO_4$, the solution was concentrated under reduced pressure to give 2.1 g (10.7 mmol, 97%) of 2-chloro-8-methoxyquinoline (**34**) as a white solid: mp 77−78 °C; IR (neat) 1591, 1566, 1496, 1465, 1418, 1263, 1122, and 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 3H), 7.09 (dd, 1H, J = 0.8 Hz, J = 7.9 Hz), 7.37 (d, 1H, J = 7.9 Hz), 7.39 (t, 1H, J = 8.4 Hz), 7.48 (t, 1H, J = 8.4 Hz), and 8.79 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 108.9, 119.3, 123.1, 127.3, 128.0, 138.9, 139.5, 149.9, and 154.6.

To 3.0 mL of fuming HNO_3, freshly distilled at reduced pressure from a 1:1 mixture of 70% HNO_3/H_2SO_4, keeping the bp < 70 °C, was carefully added 1.0 mL of concentrated H_2SO_4 at 0 °C. To this mixture was added 0.5 g (2.6 mmol) of 2-chloro-8-methoxyquinoline (**34**) in portions over 2 min at 0 °C. After stirring under a dry nitrogen atmosphere for 2 h at 0 °C, the mixture was carefully poured over 50 mL of crushed ice. The resulting solid was filtered, washed with ice-cold water, and dried overnight under high vacuum to give 0.51 g (70%) of 2-chloro-8-methoxy-5,7-dinitroquinoline (**35**): mp 114−116 °C; IR (neat) 1590, 1523, 1397, and 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 3H), 7.78 (d, 1H, J = 9.2 Hz), 8.84 (s, 1H) and 9.17 (d, 1H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.6, 121.5, 123.7, 128.0, 135.9, 138.8, 140.2, 142.5, 152.7, and 154.9. HRMS Calcd for $[C_{10}H_6ClN_3O_5 + H^+]$: 284.0074. Found: 284.0079.

Preparation of 9-Benzyl-1-chloro-4-methyl-9*H*-β-carboline (40). To a stirred solution of 0.5 g (2.0 mmol) of 1-benzyl-1*H*-indole-2-carboxylic acid in 8 mL of benzene containing 2 drops of *N*,*N*-dimethylformamide was added 0.26 mL (2.0 mmol) of oxalyl chloride. The resulting solution was stirred at rt for 3 h, after which time the solvent was removed under reduced pressure, and the residue was taken up in 10 mL of CH_2Cl_2. To this solution were added 1 mL of pyridine and 0.41 g (2 mmol) of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide dissolved in 3 mL of CH_2Cl_2. The solution was allowed to stir at rt overnight. The solution was then quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with aq 10% HCl, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.72 g (81%) of *N*-(1-benzyl-1*H*-indole-2-carbonyl)-4-methyl-*N*-prop-2-ynylbenzenesulfonamide (**42**) as a pale yellow oil: IR (neat) 3290, 3060, 2924, 2127, 1673, 1596, 1514, 936, and 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (t, 1H, J = 2.4 Hz), 2.45 (s, 3H), 4.55 (d, 2H, J = 2.8 Hz), 5.49 (s, 2H), 7.01 (m, 2H), 7.22 (m, 4H), 7.34 (m, 5H), 7.74 (d, 1H, J = 8.0 Hz) and 7.90 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 38.5, 47.9, 73.9, 78.9, 110.7, 111.0, 121.4, 123.2, 125.9, 126.2, 127.2, 127.8, 128.9, 129.1, 129.7, 129.9, 135.7, 137.9, 139.5, 145.3, and 163.9. HRMS Calcd for $[C_{26}H_{22}N_2O_3S + H^+]$: 443.1429. Found: 443.1425.

A 0.44 g (1 mmol) sample of indole **42** was stirred with 15 mg of Au(III) chloride in 10 mL of CH_2Cl_2 at rt overnight. The mixture was filtered through a plug of silica gel, washed with triethylamine, and rinsed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.36 g (82%) of 9-benzyl-4-methyl-2-(4-methylbenzenesulfonyl)-2,9-dihydro-β-carbolin-1-one (**43**) as a white solid: mp 181−182 °C; IR (neat) 3107, 3063, 2925, 1668, 1598, 1366, 1174, 1089, and 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.60 (d, 3H, J = 0.8 Hz), 5.93 (s, 2H), 7.01 (m, 2H), 7.12 (m, 3H), 7.22 (m, 1H), 7.34 (m, 4H), 7.72 (d, 1H, J = 1.2 Hz), 8.00 (d, 2H, J = 8.4 Hz) and 8.06 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 21.9, 48.1, 111.5, 113.4, 120.1, 121.3, 122.3, 123.2, 125.8, 126.0, 127.2, 127.4, 127.5, 128.7, 129.6, 129.7, 134.9, 137.9, 141.1, 145.6 and 154.7. Anal. Calcd for $C_{26}H_{22}N_2O_3S$: C, 70.57; H, 5.01; N, 6.33. Found: C, 70.43; H, 4.82; N, 6.45.

To a solution of 25 mg (0.06 mmol) of **43** in 2 mL of dry THF was added a 1.3 M solution of sodium naphthalenide in 1,2-dimethoxyethane (freshly prepared from sodium metal and naphthalene) dropwise at −78 °C until the green color persisted for more than 2 min. The solution was stirred for 30 min at −78 °C and then quenched with a saturated aqueous solution of NH_4Cl. After the addition of 5 mL of water, the mixture was extracted with CH_2Cl_2, and the extracts were dried over $MgSO_4$. The mixture was filtered, the solvent was removed under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 13 mg (82%) of 9-benzyl-4-methyl-2,9-dihydro-β-carbolin-1-one (**44**) as a white solid: mp 256−258 °C; IR (neat) 2965, 2939, 1644, 1622, 1456, 1435, 744, and 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H), 6.12 (s, 2H), 6.91 (s,1H), 7.23 (m, 6H), 7.43 (t, 1H, J = 7.2 Hz), 7.62 (d, 1H, J = 8.8 Hz), 8.11 (d, 1H, J = 8.4 Hz) and 11.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 48.1, 111.2, 113.1, 120.5, 121.9, 122.9, 123.2, 126.4, 126.6, 126.8, 127.2, 127.4, 128.8, 138.6, 140.5 and 157.0. Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.13; H, 5.60; N, 9.72. Found: C, 79.28; H, 5.46; N, 9.78.

A 0.29 g (1 mmol) sample of **44** in 5 mL of $POCl_3$ was heated at reflux for 24 h. The solution was slowly quenched with a saturated aqueous solution of $NaHCO_3$ and then extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.23 g (76%) of 9-benzyl-1-chloro-4-methyl-9*H*-β-carboline (**40**) as a white solid: mp 157−159 °C; IR (neat) 3033, 1616, 1562, 1496, 1444, 1060, 954, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H), 5.96 (s, 2H), 7.04 (m, 2H), 7.22 (m, 3H), 7.32 (t, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.56 (t, 1H, J = 8.4 Hz), 7.99 (s, 1H) and 8.20 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 47.9, 110.6, 120.9, 121.9, 123.7, 126.2, 127.2, 127.6, 128.7, 129.0, 130.7, 131.2, 132.1, 137.9, 139.0, and 142.3. Anal. Calcd for $C_{19}H_{15}N_2Cl$: C, 74.49; H, 4.94; N, 9.15. Found: C, 74.45; H, 4.78; N, 8.99.

Preparation of 9-Benzyl-1-(8-methoxy-5,7-dinitroquinolin-2-yl)-4-methyl-9*H*-β-carboline (41). To a solution of the above β-carboline **40** (0.15 g, 0.5 mmol) in 5 mL of dry toluene were added 2-tri-*n*-butylstannyl-8-methoxy-5,7-dinitroquinoline (**36**) (0.27 g, 0.5 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (35 mg, 0.05 mmol) under an argon atmosphere. The mixture was heated at 100 °C for 3 h and cooled to rt, water was added, and the mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.13 g (63%) of the titled compound **41** as a light yellow solid: mp 215−217 °C, IR (neat) 2924, 2854, 1570, 1528, 1246, and 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (s, 3H), 4.36 (s, 3H), 5.81 (s, 2H), 6.01 (d, 2H, J = 7.6 Hz), 6.75 (t, 2H, J = 8.0 Hz), 6.92 (t, 1H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.2 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.65 (t, 1H, J = 7.2 Hz), 8.00 (d, 1H, J = 8.8 Hz), 8.37 (d, 1H, J = 8.0 Hz), 8.40 (s, 1H), 8.86 (s, 1H) and 8.92 (d, 1H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 48.8, 65.7, 110.4, 120.8, 120.9, 122.1, 123.9, 124.1, 125.1, 127.3, 128.4, 128.5, 128.7, 128.9, 130.7, 132.5, 134.2, 136.3, 139.1, 139.4, 140.0, 140.2, 141.5, 143.1, 155.9 and 159.2. Anal. Calcd for $C_{29}H_{21}N_5O_5$: C, 67.03; H, 4.08; N, 13.49. Found: C, 66.92; H, 3.94; N, 13.58.

Preparation of 5,7-Dibromo-2-chloro-8-hydroxyquinoline (45). To a solution of 0.5 g (2.8 mmol) of 2-chloro-8-quinolinol (**32**) in 10 mL of methanol/CH_2Cl_2 (1:1) was added 0.7 g (8.4 mmol) of $NaHCO_3$. A solution of 1.33 g (8.4 mmol) of Br_2 in 10 mL of MeOH/CH_2Cl_2 (1:1) was slowly added dropwise at room temperature to the above solution. After the addition, the mixture was stirred for another 30 min at room temperature and was quenched by the addition of aqueous Na_2SO_3. To this mixture was added 50 mL of CH_2Cl_2, and the heterogeneous solution was filtered. The filtrate was washed with water and extracted with CH_2Cl_2. Removal of the solvent under reduced pressure afforded a yellow solid which was purified by silica gel chromatography to give 0.82 g (87%) of 5,7-dibromo-2-chloro-8-hydroxyquinoline (**45**) as a white solid: mp 155−156 °C; IR (neat) 3355, 1572, 1479, 1444, 1340, and 1309 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 8.7 Hz), 7.91 (s, 1H), 8.07 (s, 1H), and 8.39 (d, 1H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.0, 110.3, 124.4, 125.5, 134.4, 138.1, 139.2, 148.9, and 151.1. HRMS Calcd for [$C_9H_4Br_2ClNO$) + H^+]: 335.8427. Found: 335.8421.

Preparation of 2-Chloro-7-bromoquinoline-5,8-dione (46). To a solution of 1.9 g (5.6 mmol) of 5,7-dibromo-2-chloro-8-hydroxyquinoline (**45**) in 4.0 mL of concentrated sulfuric acid was added 1.2 mL of HNO_3 (aq 70%) at 0 °C over a 5 min period. After stirring for 30 min at 0 °C, the solution was poured over ice and extracted with CH_2Cl_2. The resulting solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 1.1 g (77%) of 7-bromo-2-chloroquinoline-5,7-dione (**46**) as a yellow solid: mp 187−188 °C; IR (neat) 1692, 1654, 1572, and 1309 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.98 (d, 1H, J = 8.9 Hz), and 8.38 (d, 1H, J = 8.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 128.0, 129.1, 137.9, 139.1, 139.9, 147.0, 154.7, 174.9, and 181.6. HRMS Calcd for [$C_9H_3BrClNO_2$) + H^+]: 271.9114. Found: 271.9113.

Preparation of 7-Amino-2-chloroquinoline-5,8-dione (47). To a solution of 0.16 g (0.57 mmol) of 7-bromo-2-chloroquinoline-5,8-dione (**46**) in 15 mL of acetone at −30 °C was added 39 mg (0.60 mmol) of sodium azide under a dry nitrogen atmosphere. After stirring for 1 h at −30 °C, the solution was allowed to warm to 0 °C and was rapidly chromatographed on silica gel to give 70 mg (52%) of 7-azido-2-chloro-quinoline-5,8-dione as an orange solid which was immediately subjected to reduction. To a solution of 0.18 g (0.75 mmol) of the crude 7-azido-2-chloro-quinoline-5,8-dione in 5 mL of CH_2Cl_2 was added a solution of 0.21 g (0.78 mmol) of PPh_3 in 2 mL of CH_2Cl_2 at 0 °C over a 10 min period. After stirring for an additional 20 min at 0 °C, 2 mL of an aqueous 0.5 M HCl solution was added to the mixture. After stirring for 30 min at 0 °C, the mixture was treated with Et_3N to obtain a neutral pH (pH 7). Subsequently, the organic solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to give 62 mg (22%) of 7-amino-2-chloroquinoline-5,8-dione (**47**) as a dark red solid: mp 279−280 °C; IR (neat) 3457, 1693, 1629, 1563, 1436, 1377, and 1339 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.84 (s, 1H), 7.20−7.60 (brs, 2H), 7.88 (d, 1H, J = 8.3 Hz), and 8.27 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 101.4, 129.1, 129.3, 137.1, 146.9, 151.1, 153.0, 178.9, and 179.9. HRMS Calcd for [$C_9H_5ClN_2O_2$) + H^+]: 209.0118. Found: 209.0116.

5,7-Diacetamido-8-methoxy-2-(5-methylpyridin-2-yl)quinoline (50). To a suspension of finely powdered 2-(5-methylpyridin-2-yl)-8-methoxy-5,7-dinitroquinoline (**31**) (0.34 g, 1 mmol) in 2 mL of MeOH was added a catalytic amount of Pd/C. The mixture was subjected to hydrogenation (30 psi) for 15 h using a Parr hydrogenator. The reaction mixture was filtered and washed with MeOH, and the solvent was removed under reduced pressure to afford quinoline **49** as a brown solid. Without purification, the solid material was taken up in 5 mL of CH_2Cl_2, and to this solution was added acetic anhydride (0.19 mL, 2 mmol) and Et_3N (0.28 mL, 2 mmol). The mixture was stirred overnight at room temperature, water was added, and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic extracts were filtered and evaporated under reduced pressure to give 0.33 g (89%) of 5,7-diacetamido-8-methoxy-2-(5-methylpyridin-2-yl)quinoline (**50**): mp 273−274 °C; IR

(neat) 3013, 2985, 1669, 1523, 1312, 854, and 730 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.17 (s, 3H), 2.20 (s, 3H), 2.41 (s, 3H), 4.21 (s, 3H), 7.88 (dd, 1H, J = 8.0 and 2.0 Hz), 8.41 (s, 1H), 8.45 (s, 2H), 8.54 (d, 1H, J = 8.4 Hz), 8.60 (t,1H, J = 0.8 Hz), 9.67 (s, 1H) and 10.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.6, 23.9, 24.7, 62.8, 117.1, 118.9, 121.3, 121.7, 129.1, 129.6, 131.6, 134.0, 135.0, 138.5, 142.0, 150.3, 153.4, 155.2, 169.7 and 169.8. Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.91; H, 5.54; N, 15.38. Found: C, 65.68; H, 5.47; N, 15.03.

7-Acetamido-2-(5-methylpyridin-2-yl)quinoline-5,8-dione (51). A solution of CAN (0.21 g, 0.4 mmol) in 1 mL of water was added to a solution of quinoline **50** (0.07 g, 0.2 mmol) in 1.5 mL of CH_3CN at 0 °C. After stirring for 10 min at 0 °C, water was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give the titled compound **51** as a yellow solid (57 mg, 93%): mp 247−249 °C; IR (neat) 3352, 2941, 1672, 1518, 1334, 833, and 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.45 (s, 3H), 7.71 (d, 1H, J = 9.2 Hz), 7.97 (s, 1H), 8.45 (brs, 1H), 8.53 (m, 3H) and 8.83 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 25.3, 116.8, 122.4, 125.7, 129.1, 135.4, 135.5, 137.9, 140.7, 145.8, 150.2, 151.7, 160.7, 169.7, 179.6 and 184.7. Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.43; H, 4.27; N, 13.68. Found: C, 66.57; H, 4.14; N, 13.57.

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Supporting Information Available: Spectroscopic and experimental procedures for compounds **11**−**15**, **17**, **22**−**24**, and **37**−**39**, as well as ^1H and ^{13}C NMR data of various key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.