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Synthesis of 5-Substituted-1*H*-indol-2-yl-1*H*-quinolin-2-ones: A Novel Class of KDR Kinase Inhibitors

Jeffrey T. Kuethe,* Audrey Wong, Chuanxing Qu, Jacqueline Smitrovich, Ian W. Davies, and David L. Hughes

Department of Process Research, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

jeffrey_kuethe@merck.com

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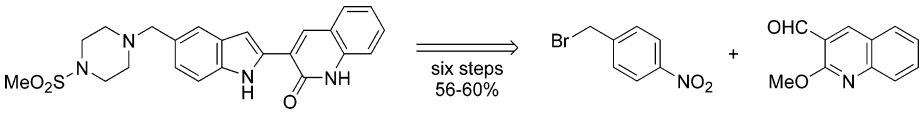
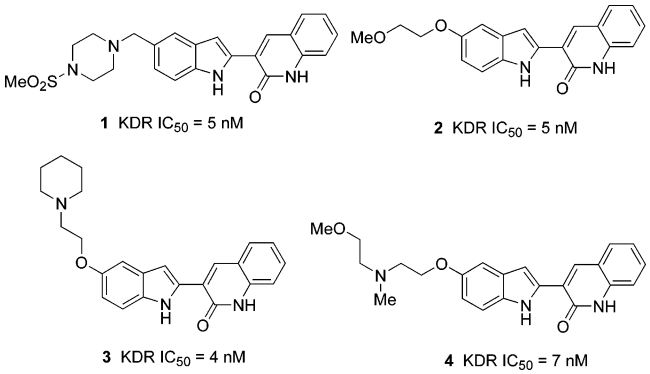


A number of approaches for the synthesis of the 1*H*-indol-2-yl-1*H*-quinolin-2-one ring system found in the potent and selective KDR kinase inhibitor **1** are described. The preparation and reaction of trimethylsilylnitrobenzene **26** with 2-methoxy-3-quinolinecarboxaldehyde **28** afforded alcohol **30**, which was the key intermediate for the preparation of the target compounds. Conversion of alcohol **30** to either nitroketone **36** or nitrostyrene **45** set the stage for reductive cyclization and the formation of indole **25**. The quinolin-2-one functionality was unmasked in the last step to provide compound **1** in 56−60% overall yield from readily available starting materials.

Tyrosine kinases are a class of enzymes which are believed to play a critical role in signal transduction in a number of cellular functions and have been implicated in a wide range of diseases and conditions including angiogenesis, cancer, tumor growth, atherosclerosis, diabetic retinopathy, and inflammatory diseases to name a few.[1] The kinase insert domain receptor (KDR) is a tyrosine kinase that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor induced angiogenesis.[2] Compounds which inhibit, modulate, or regulate the KDR receptor are useful for the prevention and treatment of tumor induced angiogenesis. As part of a program to discover and develop inhibitors of KDR kinase activity, Merck has identified a number of potent and selective KDR inhibitors such as compounds **1**−**4**.[3−5] The key



structural feature of these molecules is the indol-2-yl quinolin-2-one ring system bearing a substituent in the 5-position of the indole ring. In this Article we describe our synthetic efforts toward the construction of the indol-2-yl-quinolin-2-one ring system, the key pharmacophore present in compounds **1**−**4**.[6]

Results and Discussion

The indole nucleus is probably the most widely distributed heterocyclic ring system found in nature. Due to the existence of a vast array of structurally diverse

(1) (a) Carmeliet, P.; Jain, R. K. *Nature* **2000**, *407*, 249. (b) Folkman, J. *Nature Med.* **1995**, *1*, 27. (c) Zetter, B. R. *Annu. Rev. Med.* **1998**, *49*, 407. (d) Folkman, J. *N. Engl. J. Med.* **1995**, *333*, 1757. (e) Traxler, P. *Expert Opin, Ther. Targets* **2003**, *7*, 215 and references therein.

(2) (a) Veikkola, T.; Karkkainen, M.; Claesson-Welsh, L.; Alitalo, K. *Cancer Res.* **2000**, *60*, 203. (b) Thomas, K. A. *J. Biol. Chem.* **1996**, *271*, 603.

(3) Fraley, M. E.; Antanavage, J.; Arrington, K. L.; Ciecko, P. A.; Coll, K. E.; Gribbs, J. B.; Hambaugh, S. R.; Hartman, G. D.; Heimbrook, D. C.; Hoffman, W. F.; Hungate, R. W.; Kohl, N. E.; Mao, X.; McFall, R. C.; Rands, E.; Rickert, K.; Sepp-Lorenzino, L.; Shipman, J. M.; Tebben, A. J.; Thomas, K. A. Presented at the 224th National Meeting of the American Chemical Society, Boston, MA, Sept. 2002; Abstract MEDI-221.

(4) (a) De-Feo-Jones, D.; Helmbrook, D. C.; Jones, R. E. U.S. Patent US2002/0041880 A1, 2000. (b) Fraley, M. E.; Arrington, K. L.; Bilodeau, M. T.; Hartmen, G. A.; Hoffman, W. F.; Kim, Y.; Hungate, R. W. U.S. Patent, 6,306,874 B1, 2001. (c) Merck & Co., Inc. World Intellectual Property Organization Patent WO 087651, 2004.

(5) Fraley, M. E.; Hoffman, W. F.; Arrington, K. L.; Hungate, R. W.; Hartman, G. D.; McFall, R. C.; Coll, K. E.; Rickert, K.; Thomas, K. A.; McGaughey, G. B. *Curr. Med. Chem.* **2004**, *11*, 709.

(6) For a preliminary account of the preparation of compounds **2**−**4**, see: Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975.

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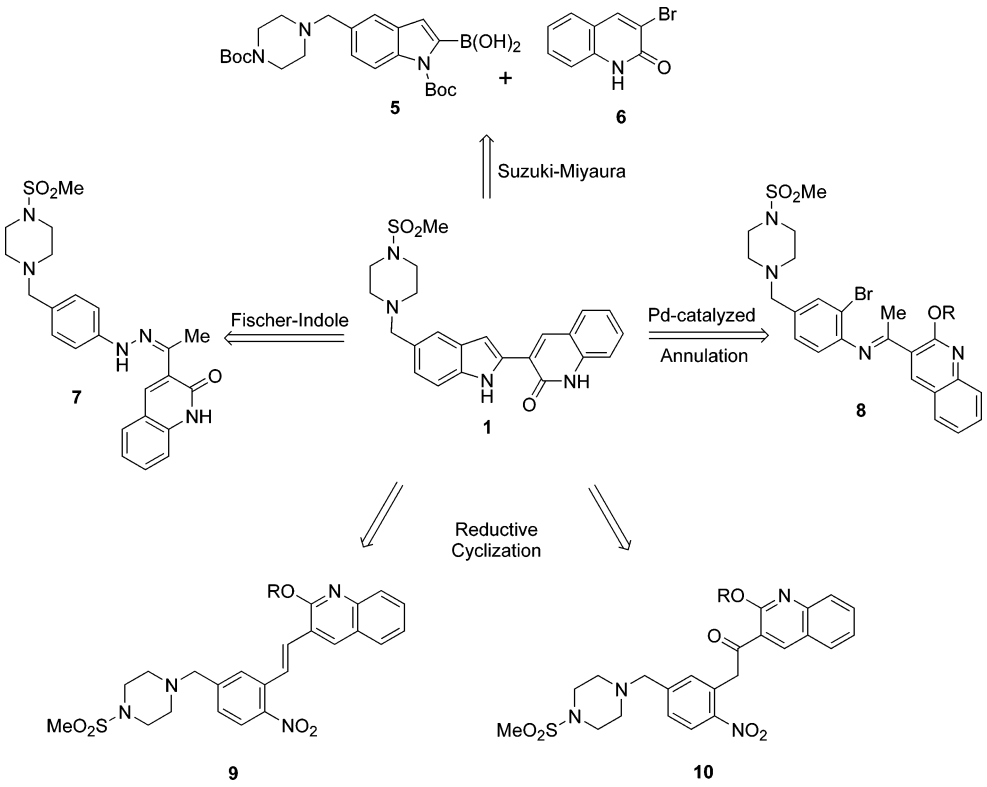
SCHEME 1



and biologically active indoles, it is not surprising that the indole nucleus is an important feature in many medicinal agents.[7] Conventional approaches to 2-aryl indoles typically rely upon cross coupling of 2-indolyl halides, boronic acids, or stannanes and silanes.[8] Although effective methods are available for the preparation of 2-indolyl boronic acids and silanes,[9] the major limitation with most of these approaches is the additional steps needed for the preparation of the coupling partners to enter the palladium-catalyzed reaction. A number of innovative methods for the synthesis of indoles have been developed;[10] however, many have limitations due to harsh reaction conditions which may interfere with other sensitive functionality often located within the target molecule. Therefore, mild synthetic methods which provide rapid assembly of the indole ring and tolerate a wide range of functional groups continue to offer significant advantages.

Retrosynthetic analysis of **1** revealed there may be a number of intriguing methods of constructing the indol-2-yl-quinolin-2-one ring system (Scheme 1). The Suzuki−Miyaura cross coupling of indolyl boronic acid **5** and 3-bromo-1*H*-quinolin-2-one **6** for the synthesis of **1** has previously been described.[4b,11] Using this cross-coupling approach, a great deal of effort was pre-invested in the preparation of appropriately functionalized 5-substituted indole **5**, which in this case may be assembled via a Fischer indole reaction of *p*-bromophenylhydrazone, cyanation, reduction, and finally amination with a protected piperazine moiety. Formation of the iodoquinolinone **6** was a two-step process. After the cross-coupling step, two additional steps were required to complete the synthesis. Approaches which centered on the formation of the indole ring as the key step for the preparation of **1**−**4** were particularly attractive. Reactions leading to increasing molecular complexity are important synthetic tools, and it was envisioned that construction of the indole ring as the key synthetic step would allow for the preparation of intermediates from readily available starting materials. For example, the indole ring could be prepared by a

(7) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Sundberg, R. J. Pyrroles and Their Benzoderivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 4, pp 313−376. (c) Sundberg, R. J. In *Best Synthetic Methods*, *Indoles*; Academic Press: New York, 1996; pp 7−11. (d) Joule, J. A. Indole and its Derivatives. In *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; George Thieme Verlag: Stuttgart, Germany, 2000; Category 2, Vol. 10, Chapter 10.13. (e) Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972.

(8) (a) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025. (b) Danieli, B.; Lesma, G.; Martinelli, M.; Passarell, D.; Perettlo, I.; Silvani, A. *Tetrahedron* **1998**, *54*, 14081. (c) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. (d) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054. (e) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1988; Chapter 10. (f) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (g) Mowery, M.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1648. (h) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (i) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (j) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221. (k) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61. (l) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649.

(9) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

(10) (a) Gribble, G. W. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 1045 and references therein. (b) Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417.

(11) (a) Payack, J.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175. (b) For the synthesis of a related compound utilizing the same stategy, see: Fraley, M. A.; Arrington, K. L.; Buser, C. A.; Ciecko, P. A.; Coll, K. E.; Fernandes, C.; Hartman, G. D.; Hoffman, W. F.; Lynch, J. J.; McFall, R. C.; Rickert, K.; Singh, R.; Smith, S.; Thomas, K. A.; Wong, B. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 351.

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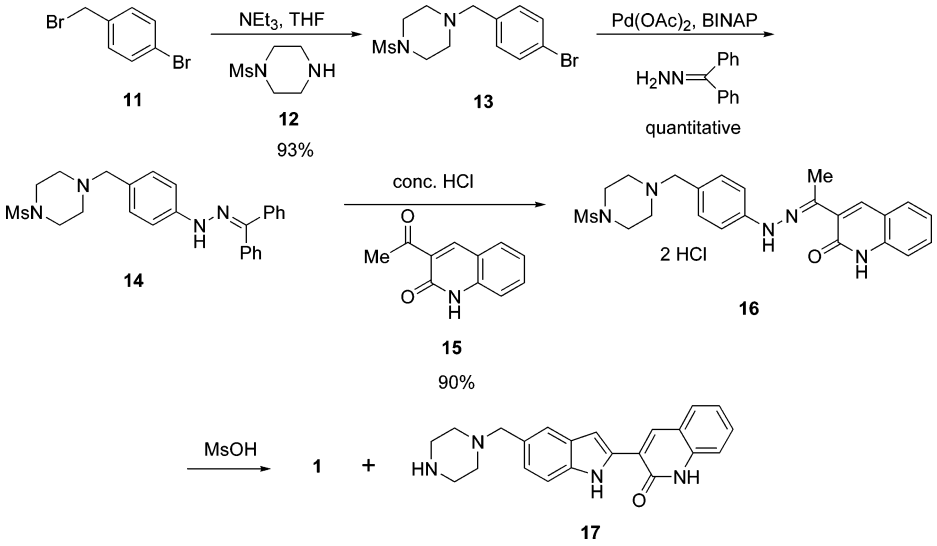


Fischer-indole cyclization of hydrazone **7**, by a palladium-mediated annulation of bromoimine **8**, or reductive cyclization of nitro styrene **9** or nitro ketone **10**. Each of these routes offered the possibility of improved synthetic efficiency and would provide the indol-2-yl-quinolin-2-one ring system of the target molecules in a limited number of synthetic steps and better atom economy. Due to the insoluble properties associated with the 1*H*-quinolin-2-one ring system of **1** and all related intermediates, the readily available and easily hydrolyzed methoxy and chloro protected quinolines were employed for the palladium-mediated annulation and reductive cyclization approaches. These quinolinone protecting groups were a key design feature and imparted a significant degree of solubility to synthetic intermediates.

Fischer-Indole Approach. Of the many methods developed for the synthesis of indoles, the Fischer-indole reaction is perhaps the most employed method and involves the acid-mediated or thermal sigmatropic rearrangement of an *N*-arylhydrazone.[12] It was envisioned that rearrangement of hydrazone **7** would provide the desired 1*H*-indol-2-yl-1*H*-quinolin-2-one ring system of **1** in four linear steps (Scheme 2). To this end, reaction of 4-bromobenzyl bromide **11** with 1-methanesulfonylpiperazine (**12**)[13] gave bromide **13** in 91% yield. Palladium-catalyzed cross coupling of **13** with benzophenone hydrazone in the presence of $Pd(OAc)_2$/BINAP[14] provided hydrazone **14** in quantitative yield. Hydrolysis of **14** with concentrated HCl in the presence of ketone **15** afforded hydrazone **16** in 90% isolated yield as the dihydrochloride salt. After considerable experimentation with a variety of Brönsted and Lewis acids in a number of solvent systems, it was found that the best conditions for effecting the desired Fischer-cyclization to the corresponding indole required refluxing in methanesulfonic acid (MsOH) for very short periods of time (<10 min). Under these conditions compound **1** could be obtained in 45% yield. The major byproduct of the reaction was identified as secondary amine **17**[11a] (40%) where the sulfonamide group was hydrolyzed under the harsh reaction conditions. When the reaction was carried out at lower temperatures, no conversion to **1** was observed, and longer reaction times resulted in increased amounts of **17** together with numerous unidentified byproducts. Under standard Fischer-indole cyclization conditions in the presence of either a catalytic or a stoichiometric amount of acid (HCl, H_2SO_4, TsOH, AcOH, TFA, H_3PO_4), Lewis acid ($ZnCl_2$, $BF_3{\cdot}OEt_2$, PCl_3, P_2O_5), or under thermal conditions (sealed tube) either no reaction or significant decomposition to unidentified byproducts was observed.

Palladium-Catalyzed Annulation Approach. The cyclization of ortho-substituted anilines has been a popular method for the construction of the indole nucleus. For example, indoles have been prepared by palladium-catalyzed cyclization of *o*-alkynylanilines under acidic[15] and basic conditions[16] or by radical cyclization of *o*-alkenylbenzonitriles.[17] Alternatively, *o*-haloanilines have served as useful precursors to indoles by palladium cross-coupling reaction followed by Rh-catalyzed hydroformylation of the Heck adducts.[18] The indole nucleus has also been prepared from *o*-haloanilines by other palladium-catalyzed couplings.[19] Recently, the photostimulated reactions of *o*-iodoanilines with carbanions by an $S_{RN}1$ mechanism for the preparation of 2-substituted and fused indoles have been reported.[20] While each of these meth-

(12) For reviews on the Fischer indole reaction, see: (a) Robinson, B. *The Fischer Indole Synthe*sis; Wiley-Interscience: New York, 1982. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, *25*, 607. (c) Gribble, G. W. *Contemp. Org. Synth.* **1994**, *1*, 1 and references therein.

(13) Jacob, R. M. German Patent DE 828695, 1950.

(14) (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

(15) Cachi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289.

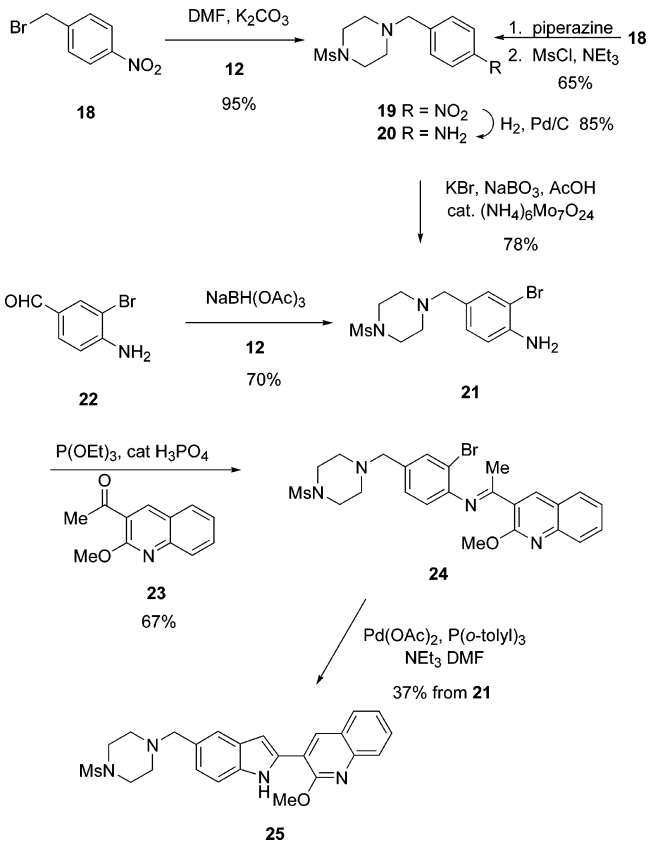
(16) (a) Kondo, Y.; Sakamoto, H. *Heterocycles* **1989**, *29*, 1013. (b) Kondo, Y.; Kojima, S.; Sakamoto, H. *J. Org. Chem.* **1997**, *62*, 6507.

(17) Fukuyama, T.; Chen, X.; Peng, G. A. *J. Am. Chem. Soc.* **1994**, *116*, 3127.

(18) Dong, Y.; Busacca, C. A. *J. Org. Chem.* **1997**, *62*, 6464.

(19) (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (b) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927. (c) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (e) Larock, R. R.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482. (f) Desarbre, E.; Merour, J.-Y. *Tetrahedron Lett.* **1996**, *37*, 43 and references therein. (g) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1996**, *62*, 2676.

SCHEME 3



ods was considered for the preparation of **1**, the palladium-catalyzed annulation between an *o*-haloaniline **21** and ketone **23** offered a highly convergent approach to the indol-2-yl-quinolin-2-one ring system found in **1**−**4**.

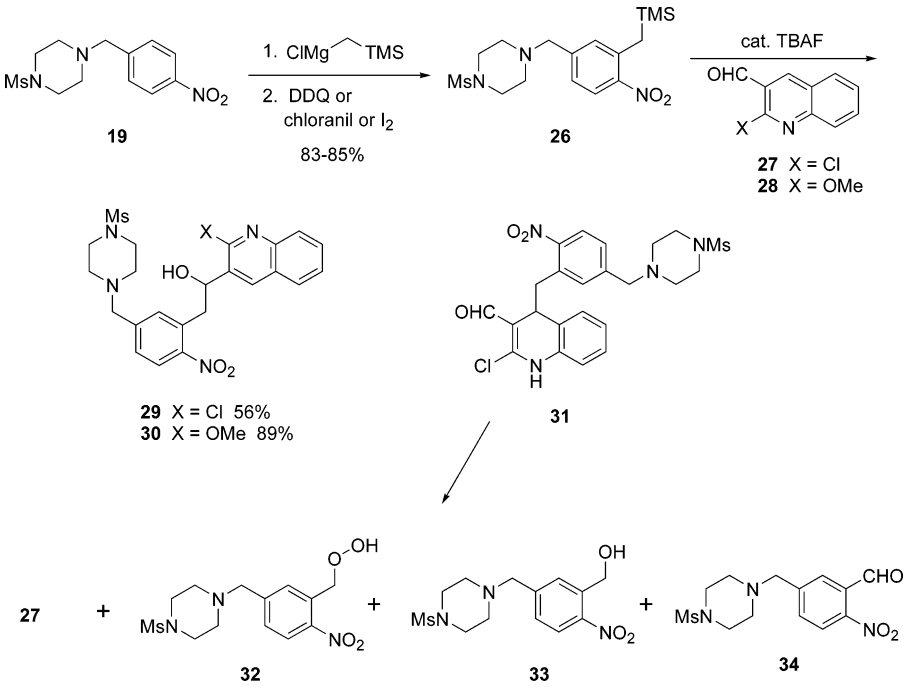
The synthesis of *o*-bromoaniline **21** began with 4-nitrobenzyl bromide **18** (Scheme 3). Reaction of **18** with **12** for 2 h in DMF in the presence of K_2CO_3 at room temperature afforded nitro derivative **19** in 95% isolated yield. Alternatively, reaction of **18** with excess piperazine followed by mesylation gave **19** in 65% overall yield. Catalytic hydrogenation of **19** gave aniline **20** (85%), which was brominated with KBr, $NaBO_3$ in the presence of a catalytic amount of $(NH_4)_6Mo_7O_{24}$ in acetic acid[21] and furnished *o*-bromoaniline **21** in 78% yield. Bromide **21** could also be prepared from aniline **22**[22] by reductive amination with sodium triacetoxyborohydride in the presence of **12** and gave **21** in 70% yield. Reaction of **21** with ketone **23** in the presence of a catalytic amount of $Pd(OAc)_2$ and DABCO[18g] did not afford indole **25**. The only detectable reaction product was aniline **20** arising from debromination of **21** under the reaction conditions. Since imine formation appeared to be problematic, efforts to convert **21** to bromoimine **24** were investigated. Reaction of **21** with **23** in refluxing toluene with water removal via either a Dean−Stark trap or molecular sieves did not afford any of the desired bromoimine **24**. Other dehydrating reagents ($MgSO_4$, Cl_2CHCO_2H, and $B(OiPr)_3$ also did not give any detectable amounts of imine **24**. When $TiCl_4$ was used as the dehydrating reagent,[23] only low conversion to **24** (30%) was noted even after prolonged reaction times. After extensive experimentation, the use of $P(OEt)_3$ as the dehydrating reagent in conjunction with a catalytic amount of H_3PO_4 in refluxing DMF afforded the best results, giving bromoimine **24** in 67% yield. Reaction of crude **24** with 3 mol % of $Pd(OAc)_2$, 3 mol % of P(*o*-tolyl)$_3$, and NEt_3 in refluxing DMF in an unoptimized process gave the methoxy-protected derivative **25** in 37% overall yield from **21**. The difficulty encountered with the formation of imine **24** and the low isolated yield of **25** made this route less attractive than other routes that were under parallel investigations (vida infra).

Reductive Cyclization of Nitro Ketone 10. Reductive cyclization of 2-nitrobenzylcarbonyl compounds is one of the oldest methods for the construction of indoles and indolinones.[7] The reductive cyclization of 2-nitrobenzylcarbonyl compounds has been carried out with a variety of reagents including H_2/Pd,[24] H_2/RaNi,[25] $SnCl_2$,[26] Fe/AcOH,[27] Zn/AcOH,[28] $TiCl_3/NH_4OAc$,[29] and $Na_2S_2O_3$.[30] However, the availability of starting materials has severely limited the utility of this approach. Recent advances by Buchwald,[29a] Rawal,[29b] RajanBabu,[31] and others[32] have given ready access to 2-nitrobenzylcarbonyl compounds which are conveniently converted to substituted indoles. While these methods are noteworthy, there is still a need for methods which provide highly functionalized 2-nitrobenzylcarbonyl compounds and their subsequent conversion to indoles. The reductive cyclization of nitroketone **36**[33] was investigated in an effort to overcome the limitations of the Fischer-indole and palladium-catalyzed annulation approaches for the synthesis of the target compound.

Our first goal was the development of an efficient synthesis of nitroketone **36**. Inspired by the unique versatility of nitrobenzenes to serve as both nucleophilic and electrophilic partners, nitrobenzene **19** was an at-

(20) Barolo, S. M.; Lukach, A. E.; Rossi, R. A. *J. Org. Chem.* **2003**, *68*, 2807 and references therein.
(21) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083.
(22) Liedholm, B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2235.
(23) Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246.
(24) (a) Cruces, J.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Heterocycles* **2000**, *53*, 1041. (b) Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, M. E.; Scott, J. W. *J. Org. Chem.* **1979**, *44*, 3748 and references therein. (c) Hengartner, U.; Valentine, D., Jr.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741. (d) Suzuki, H.; Gyoutku, H.; Yokoo, H.; Shinba, M.; Sato, Y.; Yamada, H.; Murakami, Y. *Synth. Lett.* **2000**, 1196.
(25) (a) Blair, J.; Newbold, G. T. *J. Chem. Soc.* **1955**, 2871. (b) Ruggli, P.; Dinger, A. *Helv. Chim. Acta* **1939**, 908. (c) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242.
(26) Rosenmund, P.; Haase, W. H. *Chem. Ber.* **1966**, *99*, 2504.
(27) (a) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066. (b) Owsley, D. C.; Bloomfield, J. J. *Synthesis* **1977**, 118.
(28) (a) Piper, J. R.; Stevens, F. J. *J. Heterocycl. Chem.* **1966**, *2*, 95. (b) Lindwall, H. G.; Mantell, G. J. *J. Org. Chem.* **1953**, *18*, 345.
(29) (a) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168. (b) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673. (c) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 673.
(30) (a) Clark, C. I.; White, J. M.; Kelly, D. P.; Martin, R. F.; Lobachevsky, P. *Aust. J. Chem.* **1998**, *51*, 243. (b) Finger, G. C.; Gortatowski, M. J.; Shiley, R. H.; White, R. H. *J. Am. Chem. Soc.* **1959**, *81*, 94.
(31) (a) RajanBabu, T. V.; Reedy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473. (b) RajanBabu, T. V.; Chenard, B. L.; Petti, M. A. *J. Org. Chem.* **1986**, *51*, 1704.
(32) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497.
(33) For a preliminary account of this work, see: Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 7761.

SCHEME 4



tractive starting material. Addition of trimethylsilylmethylmagnesium chloride to a solution of **19** in THF at −15 °C followed by oxidation of the resulting nitronate intermediate with DDQ[34] gave addition compound **26** in 85% yield (Scheme 4). Alternatively, the oxidation could be carried out with *p*-chloranil and gave **26** in 83% yield. The corresponding workup of each of these reactions proved difficult when conducted on a larger scale (>10 g) due to the difficulty in removing the DDQ or chloranil byproducts. After experimentation with a variety of oxidants, it was discovered that the nitronate intermediate was cleanly oxidized with aqueous 1 N iodine solution, which greatly simplified the workup and gave **26** in 85% yield. The higher purity of crude **26** after the aqueous iodine workup allowed for its use in the subsequent reaction without the need for chromatography.

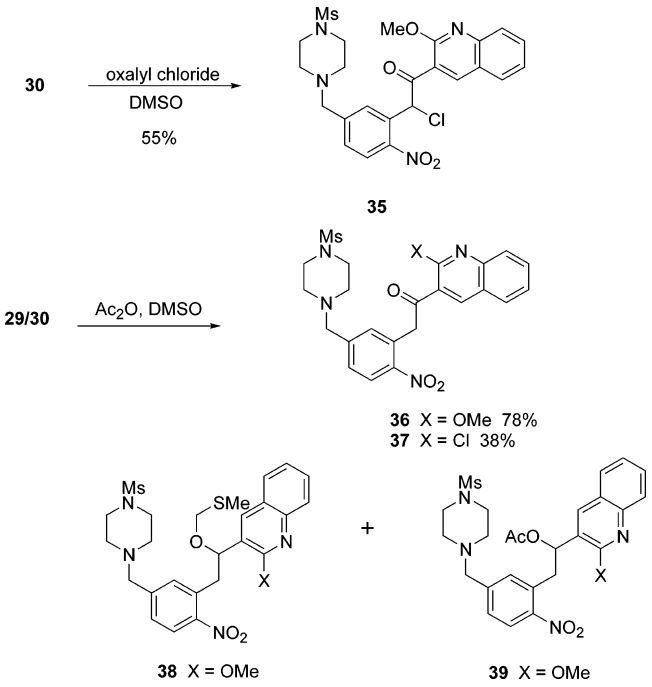
Treatment of **26** with catalytic tetrabutylammonium fluoride (TBAF, 0.10 mol %) in the presence of commercially available aldehyde **27** afforded the desired alcohol **29** in 56% isolated yield.[35] The major byproduct of this reaction was identified as 1,4-dihydroquinoline **31**. Presumably, **31** arises by addition of the carbanion to the 4-position of **27** in Michael-type fashion. Compound **31** decomposes in solution to a mixture of aldehyde **27**, peroxide **32**, alcohol **33**, and aldehyde **34**, which made the isolation of **31** difficult.[36] We speculate that retroaddition of **31** would give the nitrostabilized anion (pK_a = 25).[37] Subsequent reaction with molecular oxygen occurs to give **32**. Compounds **33** and **34** most likely are derived from the known decomposition pathways of **32**.[38] To eliminate these unwanted side reactions between the anion of **26** and the 4-position of the quinoline moiety, the electron-rich 2-methoxy-3-quinoline carboxaldehyde **28**[39] was used. Treatment of **26** with catalytic TBAF in the presence of **28** furnished alcohol **30** in 89% yield. Gratifyingly, there was no evidence of the formation of products of type **31** in the crude reaction mixture.

The oxidation of alcohols **29** and **30** was next examined. To avoid the oxidation of the piperazine nitrogen to the *N*-oxide, mild oxidative conditions were required. Oxidation of **30** under standard Swern oxidation conditions employing oxalyl chloride in DMSO[40] provided chloroketone **35** as the major product in 47% yield (Scheme 5). The formation of **35** was unexpected but not unprecedented[41] and most likely arises from deprotonation of the initially formed ketone **36** with NEt_3 followed by reaction with excess activated DMSO. On the other hand, oxidation of **30** with DMSO/Ac_2O[42] in a solution of isopropyl acetate at 80 °C provided the desired ketone **36** in 78% yield. Also detected in the crude reaction mixture was sulfide **38** (10%) and acetate **39** (3%). The formation of **38** and **39** proved to be unavoidable, but these impurities were effectively removed by the direct crystallization of **36** from the crude reaction mixture. In similar fashion, oxidation of **29** gave ketone **37** in 38% yield.

With nitroketones **36** and **37** in hand, our attention turned to the reductive cyclization of these substrates.

(34) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1986**, *51*, 3694.
(35) Bartoli, G.; Bosco, M.; Caretti, D.; Dalpozzo, R.; Todesco, R. E. *J. Org. Chem.* **1987**, *52*, 4381.
(36) Compounds **31**−**34** were identified by careful analysis of the NMR of the crude reaction mixture and by comparison to previously reported structures: see ref 6.
(37) Lelievre, J.; Farrell, P. G.; Terrier, F. *J. Chem. Soc.*, *Perkin Trans. 2* **1986**, 333.
(38) Santamaria, J.; Jroundi, R. *Tetrahedron Lett.* **1991**, *32*, 4291.
(39) Wai, J. S.; Williams, T. M.; Bamberger, D. L.; Fisher, T. E.; Hoffman, J. M.; Hudcosky, R. J.; MacTough, S. C.; Rooney, C. S.; Saari, W. S.; Thomas, C. M.; Schleif, W. A.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 249. Also see the Experimental Section.
(40) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(41) For the chlorination of ketones under Swern conditions see: Tidwell, T. T. *Synthesis* **1990**, 857 and references therein.
(42) (a) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214. (b) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416.

SCHEME 5



A variety of conditions were examined for the conversion of **36** to indole **25** (Scheme 6).[33] Optimal conditions for the conversion of **36** to **25** involved the use of 40 wt % of Ra/Ni 2800 (H_2O), 40 psi of H_2, and 65 °C in THF for 7.5 h and gave **25** in 95% yield. Other detectable impurities present in the crude reaction mixture were identified as aniline **40** (1.3%) and tolyl derivatives **41** (0.7%) and **42** (0.6%). Each of these impurities was authenticated by independent synthesis. The isolation of **25** was simply a matter of filtering the catalyst, concentrating the filtrate, and adding MeOH**,** which precipitated the product in analytically pure form in 90% isolated yield. Reaction of nitroketone **37** under the optimized reaction conditions afforded the expected indole **43** in 46% yield. However, the reductive cyclization of **37** was complicated by the further reduction of the chloroquinoline to give quinoline **44** in 23% yield.

Reductive Cyclization of Nitrostyrene 11. The reductive cyclization of aromatic nitrostyrene compounds for the formation of indoles has received considerable attention as an important synthetic tool.[43] For example, Cadogan[44] and Sundberg[45] pioneered the synthesis of a variety of substituted indoles by the deoxygenation of aromatic nitro compounds by trivalent phosphorus compounds. Triethyl phosphite is the most commonly used reagent for this transformation; however, triphenylphosphine, phosphorus trihalides, and diethoxy methylphosphine have also been employed.[46] Transition metal catalyzed reductive cyclization of aromatic nitro compounds in the presence of carbon monoxide has emerged in recent years as a highly versatile method for the construction of indoles.[47] While a number of transition metal catalysts have been employed including platinum, rhodium, ruthenium, iron, nickel, and tin complexes, complexes of palladium remain the most synthetically useful.[43,48]

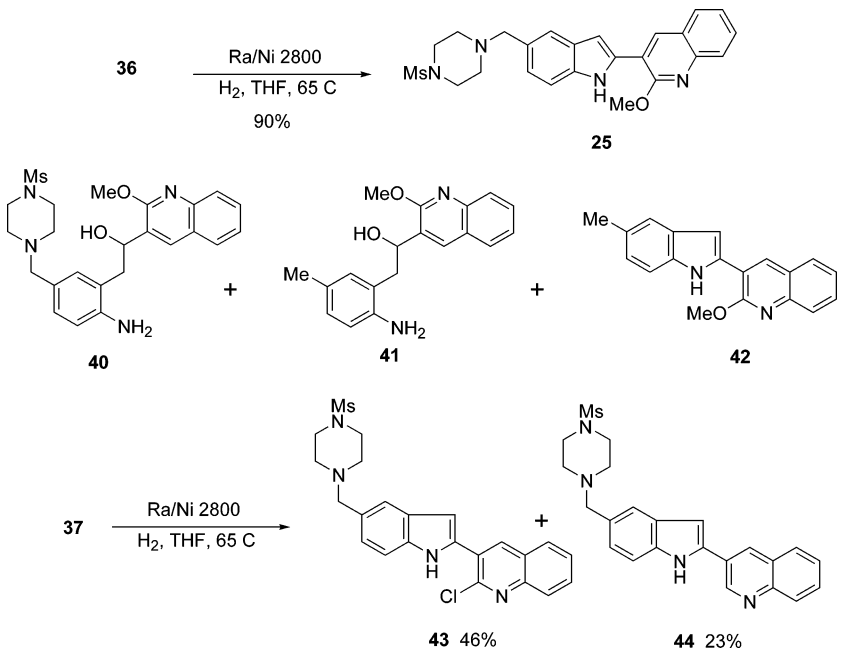
The preparation and reductive cyclization of nitrostyrene **45** is outlined in Scheme 7. Treatment of crude **30** with TFAA followed by elimination of the corresponding trifluoroacetate with DBU at 60 °C afforded *trans*-nitrostyrene **45** in 80% yield for the one-pot procedure.[49] There was no detectable amount of *cis*-nitrostyrene **47** formed in reaction, which was unequivocally established by photolysis of **45** in acetonitrile and gave a 1:1 mixture of **45** and **47** by ^{1}H NMR and HPLC analysis. In addition, the use of DBU for the elimination of the trifluoroacetate intermediate was crucial. When other alkylamine bases such as NEt_3, Hunigs base, or diisopropylamine were used, little conversion to styrene **45** was observed. The use of aqueous bases resulted in hydrolysis and alcohol **30** was re-isolated. Nitrostyrene **45** could also be prepared by cross coupling of bromide **21** with methoxy vinylquinoline **46** to give **45** in 63% yield. The reductive cyclization of **45** was verified by the classic Cadogan/Sundberg conditions,[44−47] using refluxing $P(OEt)_3$ to give indole **25** in 65% yield. When the reaction was conducted in toluene or xylene in the presence of an excess of $P(OEt)_3$, no reaction was observed. Due to the extremely high reaction temperatures and difficulty in separation of the product away from $P(OEt)_3$ and $PO(OEt)_3$, our attention turned to transition metal catalyzed processes.

Initial investigations into palladium-catalyzed reductive cyclization of **45** were conducted with the Söderberg conditions (6 mol % of $Pd(OAc)_2$, 24 mol % of PPh_3, 70 °C, 60 psi of CO).[47] These conditions afforded **25** in 95% yield. The only detectable impurity was identified as dimer **48**, which was formed in 2−3% yield. Subjection of *cis*-nitrostyrene **47** to the identical reaction conditions furnished **25** in 92% yield, thereby establishing that both *cis*- and *trans*-nitrostyrenes could be employed in the reductive cyclization reaction. Due to the high catalyst loading and difficulty in removing both triphenylphosphine oxide and indole dimer **48** without resorting to chromatography, the reaction was optimized with regard to catalyst, ligand, solvent, temperature, and CO pressure.[50] Optimized conditions involved heating **45** with 0.1 mol % of $Pd(TFA)_2$, 0.7 mol % of 3,4,7,8-tetramethylphenanthroline (TMP) in DMF at 80 °C, and 15 psi of CO and gave **25** in 95% isolated yield with no detectable amount of dimer **48**. These improved reaction conditions allowed for **25** to be isolated in analytically pure form after filtering of the reaction mixture over Celite followed by crystallization of the product by the addition of MeOH.

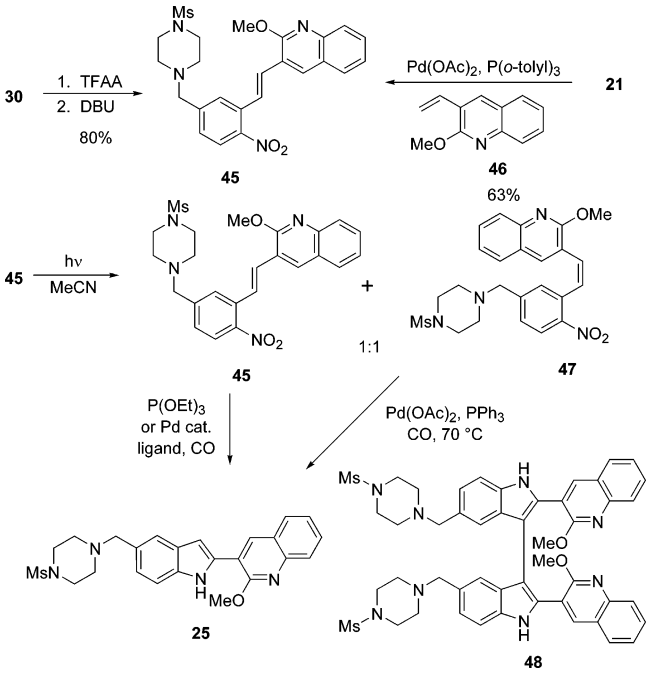
The reductive cyclization reactions of nitrostryrenes **50** and **51** were also examined (Scheme 8). Reaction of TMS-

(43) For a recent review see: Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, *4*, 727.
(44) (a) Cadogan, J. I. G.; Cameron-Wood, M. *Proc. Chem. Soc.* **1962**, 361. (b) Cadogan, J. I. G.; Mackie, R. K.; Todd, M. J. *J. Chem. Soc., Chem. Commun.* **1966**, 491.
(45) (a) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604. (b) Sundberg, R. J.; Tamazaki, T. *J. Org. Chem.* **1967**, *32*, 290.
(46) Cadogan, J. I. G.; Todd, M. J. *J. Chem. Soc.* **1969**, 2808.
(47) (a) Söderberg, B. C.; Shiver, J. A. *J. Org. Chem.* **1997**, *62*, 5838. (b) Ragaini, F.; Sportiello, P.; Cenini, S. *J. Organomet. Chem.* **1999**, *577*, 283. (c) Söderberg, B. C.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657. (d) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621. (e) Dantale, S. W.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 5507.
(48) Tolari, S.; Cenini, S.; Crotti, C.; Gianella, E. *J. Mol. Catal.* **1994**, *87*, 203.
(49) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3721.
(50) For a preliminary report see: Smitrovich, J.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533.

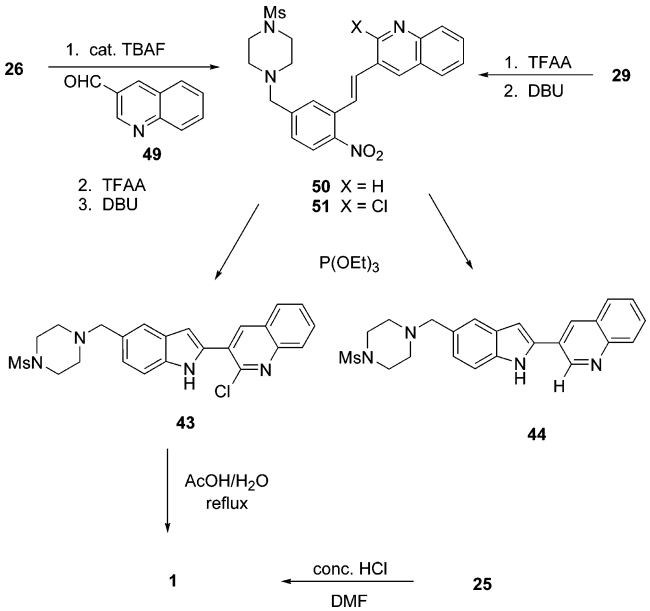
SCHEME 6



SCHEME 7



SCHEME 8



nitro compound **26** with aldehyde **49** followed by elimination gave nitrostyrene **50** in 63% overall yield. Nitrostyrene **51** (72%) was prepared in analogous fashion from alcohol **29**. Reductive cyclization of each of these compounds with $P(OEt)_3$ afforded **43** (61%) and **44** (72%). Reaction of each of these substrates under the optimized conditions for reductive cyclization of **45** (0.1 mol % of $Pd(TFA)_2$, 0.7 mol % of TMP, 15 psi of CO, DMF, 80 °C) led to low conversions to **43** and **44**, respectively.

The deprotection of the masked quinolin-2-one moiety of chloroquinoline **43** and methoxyquinoline **25** was accomplished in a straightforward manner under acidic conditions. Reaction of **25** with concentrated HCl in DMF at 70 °C gave the crystalline KDR kinase inhibitor **1** as the HCl salt in quantitative yield. Hydrolysis of chloroquinoline **43** in a 1:1 mixture of $AcOH/H_2O$ gave freebase **1** in 93% yield.

Conclusion

In summary, we have demonstrated a number of concise syntheses of the potent and selective KDR kinase inhibitor **1**. While the Fischer-indole and palladium-catalyzed annulation approaches provided access to the 1*H*-indol-2-yl-1*H*-quinolin-2-one ring system of **1**, the reductive cyclization approaches proved to be an extremely efficient and high-yielding method for construction of the target substrates. Reaction of trimethylsilyl nitro compound **26** with aldehyde **28** provided the key alcohol intermediate, which could be converted to either

nitroketone **36** or nitrostyrene **45**. Reductive cyclization of each of these intermediates followed by hydrolysis provided of the potent and selective KDR kinase inhibitor **1** in six synthetic steps from readily available bulk chemicals in 56% overall yield for the nitroketone route and 60% overall yield for the nitrostyrene route.

Experimental Section

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel, using an ethyl acetate−hexane mixture as the eluent unless specified otherwise. Water content (KF) was determined by Karl Fisher titration on a Metrohm 737 KF Coulometer.

Preparation of 1-(4-Bromobenzyl)-4-methansulfonylpiperazine (13). To a solution of 10 g (40.0 mmol) of 4-bromobenzyl bromide (**11**) in 75 mL of THF was added 7.25 mL (52.0 mmol) of NEt_3 followed by 8.94 g (48.0 mmol) of 1-methanesulfonylpiperazine[13] in 20 mL of THF. After stirring for 3 h, the reaction mixture was diluted with 75 mL of EtOAc and washed with 100 mL of water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was crystallized from an EtOAc/hexane mixture to give 12.93 g (91%) of **13** as a colorless solid: mp 105−106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53 (m, 4H), 2.77 (s, 3H), 3.21 (m, 4H), 3.48 (s, 2H), 7.18 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.2, 46.0, 52.3, 61.9, 121.2, 130.8, 131.6, 136.7. Anal. Calcd for $C_{12}H_{17}BrN_2O_2S$: C, 43.25; H, 5.14; N, 8.41. Found: C, 43.10; H, 5.12; N, 8.27.

Preparation of *N*-Benzhydrylidene-*N*′-[4-(4-methanesulfonylpiperazin-1-ylmethyl)phenyl]hydrazine (14). To a 250 mL round-bottom flask was added sequentially 100 mg (0.450 mmol) of $Pd(OAc)_2$, 420 mg (0.670 mmol) of racemic BINAP, 9.72 g (50 mmol) of benzophenone hydrazone, and 90 mL of toluene. The reaction mixture was purged (3×) with vacuum/nitrogen. The reddish solution was then heated to 105 °C for 5 min and then cooled to room temperature. To the resulting purple solution was added 15.0 g (45.0 mmol) of bromide **13** followed by 6.06 g (63.0 mmol) of sodium *tert*-butoxide. The reaction mixture was heated to 105 °C for 4 h, cooled to room temperature, and filtered over a pad of silica gel eluting with EtOAc. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography to give 20.1 g (100%) of **14** as a light yellow solid: mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (m, 4H), 2.77 (s, 3H), 3.24 (m, 4H), 3.48 (s, 2H), 7.06 (d, 2H, J = 8.4 Hz), 7.19 (d, 2H, J = 8.4 Hz), 7.34 (m, 6H), 7.53 (m, 1H), 7.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.1, 46.0, 52.5, 62.3, 112.9, 126.6, 128.2, 128.3, 128.9, 129.2, 129.4, 129.8, 130.3, 132.8, 138.4, 144.1, 144.4. Anal. Calcd for $C_{25}H_{28}N_4O_2S$: C, 66.94; H, 6.29; N, 12.49. Found: C, 67.08; H, 6.27; N, 12.15.

Preparation of 3-Acetyl-1*H*-quinolin-2-one (15). To a solution of 14.5 g (70.5 mmol) of 3-acetyl-2-chloroquinoline[48] was added 210 mL of 6 N HCl. The mixture was heated to reflux for 3 h, cooled to room temperature, and filtered over a pad of Celite. To the solution was added 750 mL of water, which precipitated the product as an orange solid. The solid was filtered and washed with water until the pH of the filtrate was 7.0. The product was dried in a vacuum oven at 40 °C under a stream of nitrogen to give 11.1 g (84%) of **15**. An analytical sample was obtained by recrystallization from EtOAc: mp 236−237 °C; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 2.58 (s, 3H), 7.19 (t, 1H, J = 7.5 Hz), 7.31 (d, 1H, J = 8.4 Hz), 7.57 (t, 1H, J = 7.1 Hz), 7.83 (d, 1H, J = 7.9 Hz), 8.42 (s, 1H), 12.08 (br s, 1H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 31.1, 115.5, 118.6, 122.8, 129.8. 130.6, 133.3, 141.0, 143.5, 160.9, 197.8. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.43; H, 4.78; N, 7.40.

Preparation of 3-(1-{[4-(4-Methanesulfonylpiperazin-1-ylmethyl)phenyl]hydrazono}ethyl)-1*H*-quinolin-2-one (16). To a slurry of 900 mg (2.00 mmol) of **14** and 410 mg (2.19 mmol) of **15** in 6 mL of a 1:1 mixture of EtOH:toluene was added 1.00 mL of concentrated HCl. The mixture was then heated to 100 °C for 12 h and cooled to room temperature, and the orange solid was filtered. The solid was washed with 1:1 EtOH:toluene (3 mL) and dried in a vacuum oven to give 820 mg (90%) of analytically pure **16**: mp 198 °C dec; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.24 (s, 3H), 2.94 (s, 3H), 3.04 (m, 2H), 3.30 (m, 4H), 3.65 (d, 2H, J = 12.7 Hz), 4.20 (s, 2H), 4.60 (br s, 2H), 7.15 (t, 1H, J = 7.4 Hz), 7.23 (d, 2H, J = 8.5 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.43 (m, 3H), 7.73 (d, 1H, J = 7.8 Hz), 8.03 (s, 1H), 11.5 (br s, 1H), 11.90 (br s, 1H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 16.3, 35.7, 42.7, 50.0, 58.9, 113.3, 115.3, 119.5, 119.8, 122.5, 128.9, 130.8, 132.3, 132.9, 137.5, 139.0, 143.5, 147.3, 161.8. Anal. Calcd for $C_{23}H_{27}N_5O_3S\cdot 2HCl$: C, 52.47; H, 5.55; N, 13.30. Found: C, 52.34; H, 5.64; N, 12.95.

Fischer-Indole Cyclization of Hydrazone 16. A slurry of 100 mg (0.230 mmol) of **16** in 2 mL of methanesulfonic acid was heated to 130 °C for 7 min. The resulting solution was cooled to room temperature and analyzed by quantitative HPLC (Zorbax SB C-18, 5 μm, 4.6 × 25 cm, 40 °C, 1.5 mL/min; Elutant A: 0.1% H_3PO_4/20 mM $NaClO_4$ pH 2.2; Eluent B: acetonitrile; time = 0 min, 80% Eluent A/20% Eluent B; time = 20 min, 60% Eluent A/40% Eluent B; time = 35 min, 40% Eluent A/60% Eluent B; retention time for **17** = 8.5 min; retention time for **1** = 14.0 min). Compound **17** (3-[5-(piperazine-1-ylmethyl)-1*H*-indol-2-yl]quinolin-2(1*H*)-one) was characterized as its bis-HCl salt after stirring the slurry in 5 N HCl and filtering the resulting solid: mp 332 °C dec; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.46 (br m, 8H), 4.42 (s, 2H), 7.20 (t, 1H, J = 7.8 Hz), 7.38 (m, 3H), 7.46 (t, 1H, J = 7.1 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.69 (d, 1H, J = 7.8 Hz), 7.81 (s, 1H), 8.61 (s, 1H), 9.90 (br s, 2H), 11.84 (s, 1H), 12.19 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 47.4, 60.0, 102.8, 112.5, 115.5, 119.9, 122.6, 122.9, 124.4, 125.5, 128.4, 130.8, 135.1, 135.4, 137.4, 138.1, 161.0. Anal. Calcd for $C_{22}H_{22}N_4O\cdot 2HCl$: C, 61.26; H, 5.61; N, 12.99. Found: C, 61.20; H, 5.59; N, 13.09.

Preparation of 1-Methanesulfonyl-4-(4-nitrobenzyl)-piperazine (19). Method A: To a slurry of 184.0 g (1.12 mol) of 1-methanesulfonylpiperazine (**12**)[13] and 118.0 g (1.12 mol) of Na_2CO_3 in 700 mL of DMF at 0 °C was added dropwise 219.0 g (1.01 mol) of 4-nitrobenzyl bromide **18** in 300 mL of DMF. After stirring for 2 h at room temperature, the reaction mixture was cooled to 10 °C and 3 L of water was slowly added via an addition funnel. The resulting slurry of the product was stirred for 1 h at room temperature and filtered, and the product was washed with an additional 500 mL of water. The product was dried in a vacuum oven at 40 °C to give 300 g (99%) of **19** as a colorless solid: mp 116−117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58 (m, 4H), 2.80 (s, 3H), 3.27 (m, 4H), 3.65 (s, 2H), 7.51 (d, 2H, J = 8.8 Hz), 8.18 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.5, 46.0, 52.6, 61.8, 123.8, 129.6, 145.7, 147.5. Anal. Calcd for $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.72; N, 14.04. Found: C, 48.16; H, 5.52; N, 13.91.

Method B: A solution of 1.0 g (4.63 mmol) of 4-nitrobenzyl bromide (**18**) in 5 mL of isopropyl acetate was added dropwise over a period of 20 min to a stirred solution of 4 g (46.4 mmol) of piperazine in 8 mL of 95% EtOH. The resulting suspension was allowed to stir at room temperature for 30 min, filtered over a pad of Celite, and concentrated under reduced pressure. The residue was dissolved in 30 mL of isopropyl acetate and washed with 25 mL of water. The isopropyl acetate layer was separated and concentrated to a final volume of 20 mL. To the solution was added 610 mg (6.01 mmol) of NEt_3 followed by 560 mg (4.86 mmol) of methanesulfonyl chloride. After stirring for 30 min the reaction mixture was filtered over a pad of Celite and concentrated to a final volume of 20 mL. To the resulting mixture was added 20 mL of heptane and the slurry of the product was stirred for 20 min and filtered affording 900 mg (65%) of **19**, which was identical to the product isolated from Method A.

Preparation of 4-(4-Methanesulfonylpiperazine-1-ylmethyl)aniline (20). To a solution of 25.0 g (83.5 mmol) of **19** in 1.50 L of EtOAc was added 5.00 g of 5% Pd/C. The resulting mixture was stirred at room temperature under an atmosphere of hydrogen (15 psi) for 4 h. The reaction mixture was filtered over a pad of Celite and concentrated under reduced pressure to give 19.0 g (84%) of 4-(4-methanesulfonylpiperazin-1-ylmethyl)aniline (**20**) as a colorless solid: mp 161−162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.52 (m, 4H), 2.76 (s, 3H), 3.22 (m, 4H), 3.42 (s, 2H), 3.67 (br s, 2H), 6.63 (d, 2H, J = 8.4 Hz), 7.06 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.1, 46.0, 52.1, 62.3, 115.0, 127.2, 130.4, 145.8. Anal. Calcd for $C_{12}H_{19}N_3O_2S$: C, 53.51; H, 7.11; N, 15.60. Found: C, 53.71; H, 7.09; N, 15.48.

Preparation of 2-Bromo-4-(4-methanesulfonylpiperazin-1-ylmethyl)aniline (21). Method A: To a solution of 7.40 g (37.0 mmol) of 4-amino-3-bromobenzaldehyde (**22**)[22] in 100 mL of CH_2Cl_2 was added 7.90 g (48.1 mmol) of 1-methanesulfonylpiperazine (**12**)[13] followed by 16.0 g (75.5 mmol) of triacetoxyborohydride. The resulting mixture was stirred for 4 h, quenched with 100 mL of saturated NH_4Cl, and extracted with 150 mL of EtOAc. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 9.01 g (70%) of **21** as a colorless solid: mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.51 (m, 4H), 2.77 (s, 3H), 3.21 (m, 4H), 3.39 (s, 2H), 4.09 (br s, 2H), 7.01 (dd, 1H, J = 8.1 and 1.7 Hz), 7.35 (d, 1H, J = 8.1 Hz), 7.78 (d, 1H, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.1, 46.0, 52.1, 61.6, 109.2, 115.6, 128.6, 129.3, 133.1, 143.4. Anal. Calcd for $C_{12}H_{18}BrN_3O_2S$: C, 41.39; H, 5.21; N, 12.07. Found: C, 41.75; H, 5.22; N, 11.67.

Method B: To a solution of 1.00 g (3.71 mmol) of **20** in 8 mL of AcOH was added sequentially 530 mg (4.45 mmol) of solid KBr, 45 mg (0.04 mmol) of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, and 600 mg (3.90 mmol) of sodium perborate. After stirring for 4 h at room temperature the reaction mixture was diluted with EtOAc and neutralized with saturated K_2CO_3 to a pH of 8.0. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was recrystallized from an EtOAc/hexane mixture to give 1.00 g (78%) of **21**, which was identical with the material prepared by Method A.

Preparation of 1-Acetyl-2-methoxyquinoline (23). To a solution of 11.0 g (53.3 mmol) of 3-acetyl-2-chloroquinoline[51] in 160 mL of MeOH was added 50 mL (0.268 mol) of a 5.4 M solution of NaOMe in MeOH. The mixture was heated to reflux for 1 h, cooled to room temperature, and diluted with 300 mL of EtOAc and 300 mL of water. The EtOAc layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 8.60 g (80%) of **23** as a colorless solid: mp 99−100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.69 (s, 3H), 4.14 (s, 3H), 7.39 (t, 1H, J = 7.3 Hz), 7.68 (t, 1H, J = 7.2 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.83 (d, 1H, J = 8.4 Hz), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.5, 53.9, 123.9, 124.6, 125.0, 127.2, 129.3, 131.9, 141.3, 148.1, 159.7, 198.5. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.52; N, 7.00.

Preparation of 2-Methoxy-3-[5-[[4-(methysulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline (25). To a solution of 500 mg (1.44 mmol) of **21** and 288 mg (1.44 mmol) of **23** in 5 mL of DMF was added 0.31 mL (1.82 mmol) of $P(OEt)_3$ and 5 μL of 85% aqueous H_3PO_4. The mixture was heated to reflux for 6 h and the solvent was removed under reduced pressure. The residue was redissolved in 8 mL of DMF and 43 mg (0.140 mmol) of P(*o*-tolyl)$_3$, 32 mg (0.140 mmol) of $Pd(OAc)_2$, and 1 mL of NEt_3 were added and the mixture heated to reflux for 6 h. The reaction mixture was cooled to room temperature and diluted with 30 mL of EtOAc and 30 mL of water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 239 mg (37%) of **25** as a light yellow solid: mp 197−198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.61 (m, 4H), 2.78 (s, 3H), 3.27 (m, 4H), 3.66 (s, 2H), 4.31 (s, 3H), 7.07 (s, 1H), 7.18 (dd, 1H, J = 8.3 and 1.4 Hz), 7.44 (m, 2H), 7.57 (s, 1H), 7.64 (t, 1H, J = 8.4 Hz), 7.81 (d, 1H, J = 8.1 Hz), 7.88 (d, 1H, J = 8.4 Hz), 8.48 (s, 1H), 9.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 46.0, 52.3, 54.1, 63.3, 101.5, 111.3, 116.8, 121.1, 124.2, 124.8, 125.5, 127.0, 127.6, 128.3, 129.0, 129.6, 134.0, 135.2, 136.0, 145.3, 158.3. Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.28; H, 5.68; N, 12.05.

Preparation of 1-Methanesulfonyl-4-(4-nitro-3-trimethylsilanylmethylbenzyl)piperazine (26). To a 5.0 L 4-neck flask equipped with a thermocouple and overhead stirrer was added 1.0 L of THF followed by 184.1 g (0.615 mol) of solid **19**. The sides of the reaction flask were rinsed with an additional 200 mL of THF and the mixture was cooled to −20 °C. To the mixture was added dropwise 800 mL of trimethylsilylmethylmagnesium chloride (0.800 mol, 1.0 M in ether) at such a rate that the internal temperature did not rise above −5 °C. The mixture was stirred for 30 min and then poured directly into 800 mL of 1 N iodine solution and stirred for 3 h at room temperature. To the biphasic reaction mixture was added 300 mL of 0.3 M $Na_2S_2O_3$ pentahydrate and 1.2 L of isopropyl acetate. The bottom aqueous layer was then removed. The organic layer was washed with 500 mL of water and then 500 mL of brine. The isopropyl acetate layer was then azeotropically dried to a Kf below 200 and a final volume of 1.3 mL in IPAC for use in the next reaction. Assay amount of **26**: 201.3 g (85%). An analytical sample could be obtained by crystallization from EtOAc/hexane: mp 57−58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.01 (s, 9H), 2.57 (m, 4H), 2.59 (s, 2H), 2.79 (s, 3H), 3.25 (m, 4H), 3.55 (s, 2H), 7.11 (s, 1H), 7.16 (d, 1H, J = 8.4 Hz), 7.90 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.40, 25.0, 34.4, 45.9, 52.4, 61.7, 125.3, 125.5, 131.7, 137.8, 143.2, 146.9. Anal. Calcd for $C_{16}H_{27}N_3O_4SSi$: C, 49.84; H, 7.06; N, 10.90. Found: C, 49.62; H, 7.08; N, 10.82.

Preparation of 2-[5-(4-Methanesulfonylpiperazin-1-ylmethyl)-2-nitrophenyl]-1-(2-chloroquinolin-3-yl)ethanol (29). To a mixture of 9.50 g (24.7 mmol) of **26** and 4.73 g (24.7 mmol) of aldehyde **27** in 175 mL of isopropyl acetate was added dropwise 6.20 mL (2.47 mmol) of a 1 M solution of TBAF. After 30 min, the reaction mixture was diluted with 100 mL of isopropyl acetate and washed with 100 mL of saturated NH_4Cl and 50 mL of water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 6.95 g (56%) of **29** as a colorless foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (m, 4H), 2.78 (s, 3H), 2.89 (d, 1H, J = 4.3 Hz), 3.13 (m, 4H), 3.48 (s, 3H), 3.55 (m, 2H), 5.55 (m, 1H), 7.34 (d, 1H, J = 1.7 Hz), 7.36 (dd, 1H, J = 8.4 and 1.7 Hz), 7.61 (m, 1H), 7.78 (m, 1H), 7.92 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.4 Hz), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.3, 40.2, 45.7, 52.2, 61.3, 70.6, 125.0, 127.3, 127.5, 127.8, 128.0, 128.1, 130.7, 132.3, 133.1, 135.5, 136.6, 143.9, 146.9, 148.5, 149.6. Anal. Calcd for $C_{23}H_{25}ClN_4O_5S$: C, 54.70; H, 4.99; N, 11.09. Found: C, 54.76; H, 4.66; N, 11.33.

Preparation of 2-Methoxyquinoline-3-carboxaldehyde (28).[39] To a solution of 5 g (75.7 mmol) of KOH in 100 mL of MeOH was added 10 g (52.2 mmol) of 2-chloro-3-quinolinecarboxaldehyde **27**. The mixture was heated to reflux for 2.5 h and then cooled to room temperature. To the solution was added 300 mL of water and the precipitated product was collected by filtration to afford 8.69 g (89%) of **28** as a tan solid. An analytical sample could be prepared by recrystallization from CH_2Cl_2/hexanes: mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (s, 3H), 7.37 (dd, 1H, J = 8.0 and 6.9 Hz), 7.67 (m, 1H), 7.76 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 8.4 Hz), 8.48 (s, 1H), 10.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.8, 120.0, 124.4, 125.0, 127.3, 129.7, 132.5, 139.9, 148.9, 161.1, 189.2. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.44; H, 4.70; N, 7.39.

(51) Bhat, B.; Bhaduri, A. P. *Synthesis* **1984**, 673.

Preparation of 2-[5-(4-Methanesulfonylpiperazin-1-ylmethyl)-2-nitrophenyl]-1-(2-methoxyquinolin-3-yl)ethanol (30). To a mixture of 5.03 g (13.0 mmol) of **26** and 2.44 g (13.0 mmol) of **28** in 60 mL of isopropyl acetate was added dropwise 3.3 mL (3.25 mmol) of a 1 M solution of TBAF. After 30 min, the reaction mixture was diluted with 35 mL of isopropyl acetate and washed with 50 mL of saturated NH_4Cl and 50 mL of water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 5.80 g (89%) of **30** as a colorless foam, which was used in the next step without further purification. An analytical sample could be obtained by chromatography on silica gel: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (m, 4H), 2.75 (s, 3H), 3.06 (m, 5H), 3.50 (m, 4H), 4.08 (s, 3H), 5.28 (t, 1H, J = 6.0 Hz), 7.11 (s, 1H), 7.29 (dd, 1H, J = 8.3 and 1.8 Hz), 7.38 (m, 1H), 7.60 (m, 1H), 7.67 (m, 1H), 7.83 (d, 1H, J = 8.3 Hz), 7.90 (d, 1H, J = 8.4 Hz), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.3, 40.4, 45.8, 52.2, 53.6, 61.5, 70.3, 124.5, 125.0, 125.2, 126.9, 127.2, 127.5, 127.8, 129.6, 133.2, 133.4, 135.1, 143.3, 145.8, 149.2, 159.4. Anal. Calcd for $C_{24}H_{28}N_4O_6S\cdot{}^1/_2H_2O$: C, 56.57; H, 5.74; N, 10.99. Found: C, 56.65; H, 5.44; N, 10.83.

2-Chloro-1-(2-methoxyquinolin-3-yl)-2-(5-{[4-(methylsulfonyl)piperazin-1-yl]methyl}-2-nitrophenyl)ethanone (35). To a solution of 910 mg (7.20 mmol) of oxalyl chloride in 3 mL of CH_2Cl_2 and was added dropwise 1.12 g (14.3 mmol) of DMSO, maintaining the internal temperature below −40 °C. After 10 min, 600 mg (1.20 mmol) of alcohol **30** in 1 mL of CH_2Cl_2 was added dropwise to the reaction mixture. The reaction was stirred for 45 min at −65 °C, and 1.90 g (19.0 mmol) of triethylamine was added dropwise and the mixture warmed to room temperature overnight. The reaction mixture was diluted with 15 mL of water and 30 mL of EtOAc. The layers were separated and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography to give 300 mg (47%) of chloride **35** as a yellow solid: mp 148−149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.52 (m, 4H), 2.79 (s, 3H), 3.21 (m, 4H), 3.63 (s, 2H), 4.16 (s, 3H), 7.42 (s, 1H), 7.47 (m, 2H), 7.75 (ddd, 1H, J = 8.4, 7.2, and 1.2 Hz), 7.80 (d, 1H, J = 1.6 Hz), 7.85 (m, 2H), 8.09 (d, 1H, J = 8.4 Hz), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.3, 45.6, 52.2, 54.0, 60.7, 61.3, 120.3, 124.2, 125.1, 125.3, 127.0, 129.0, 129.6, 131.3, 131.5, 132.5, 143.3, 144.8, 146.6, 148.1, 158.3, 190.6. Anal. Calcd for $C_{24}H_{25}ClN_4O_6S$: C, 54.08; H, 4.73; N, 10.51. Found: C, 53.94; H, 4.71; N, 10.13.

1-(2-Methoxyquinolin-3-yl)-2-(5-{[4-(methylsulfonyl)-piperazin-1-yl]methyl}-2-nitrophenyl)ethanone (36). To a heated (80 °C) solution of 19.7 g (39.4 mmol) of alcohol **30** in 79 mL of isopropyl acetate and 36.9 g (473 mmol) of DMSO was added 24.1 g (236 mmol) of acetic anhydride. The reaction mixture was heated at 80 °C for 2 h. After cooling to room temperature, the reaction was neutralized with saturated $NaHCO_3$ (175 mL) to a final pH of 8.0. The layers were separated and the organic layer was washed with water (250 mL). The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give 15.3 g (78%) of **36**. An analytical sample was obtained by recrystallization from THF/MeOH: mp 122−123.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58 (m, 4H), 2.80 (s, 3H), 3.27 (m, 4H), 3.63 (s, 2H), 4.22 (s, 3H), 4.80 (s, 2H), 7.36 (s, 1H), 7.43 (ddd, 2H, J = 1.2, 8.0, 9.2 Hz), 7.73 (ddd, 1H, J = 1.6, 6.8, 8.4 Hz), 7.85 (d, 1H, J = 15.6), 7.87 (d, 1H J = 14.7 Hz), 8.12 (d, J = 9.1), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 20.6, 34.3, 45.8, 48.8, 52.3, 53.9, 61.5, 122.9, 124.4, 124.9, 125.4, 127.0, 128.4, 129.2, 131.2, 131.9, 132.9, 133.9, 141.8, 144.2, 147.9, 159.1, 195.9. Anal. Calcd for $C_{24}H_{26}N_4O_6S$: C, 57.82; H, 5.26; N, 11.24. Found: C, 57.71; H, 5.20; N, 10.96.

2-Methoxy-3-{2-(5-{[4-(methylsulfonyl)piperazin-1-yl]-methyl}-2-nitrophenyl)-1-[(methylthio)methoxy]ethyl}-quinoline (38a). The methylthiomethyl ether **38a** was isolated after chromatography on silica gel as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (s, 3H), 2.33 (m, 4H), 2.75 (s, 3H), 3.04 (m, 4H), 3.48 (m, 4H), 4.03 (s, 3H), 4.34 (d, 1H, J = 11.6 Hz), 4.66 (d, 1H, J = 11.6 Hz), 5.41 (dd, 1H, J = 5.6, 6.4), 7.06 (d, 1H, J = 1.6 Hz), 7.29 (dd, 1H, J = 1.6, 8.8 Hz), 7.39, (ddd, 1H, J = 1.2, 6.8, 8.0 Hz), 7.63 (ddd, 1H, J = 1.2, 7.2, 8.4 Hz), 7.69 (dd, 1H, J = 1.2, 8.0 Hz), 7.83 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.4 Hz), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 34.3, 39.1, 45.6, 52.2, 53.5, 61.4, 72.4, 73.3, 124.3, 124.6, 124.8, 125.1, 127.0, 127.4, 127.5, 129.6, 132.7, 133.3, 135.3, 142.7, 145.9, 149.6, 159.8. HRMS calcd for $C_{26}H_{32}N_4O_6S_2$ 561.1836 (M + H), found 561.1808 (M + H).

1-(2-Methoxyquinolin-3-yl)-2-(5-{[4-(methylsulfonyl)-piperazin-1-yl]methyl}-2-nitrophenyl)ethyl Acetate (39a). To a solution of 500 mg (1.00 mmol) of alcohol **30** in 2 mL of isopropyl acetate was added 5.80 g (57.0 mmol) of acetic anhydride. The reaction was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, diluted with an additional 5 mL of isopropyl acetate, and neutralized with saturated $NaHCO_3$ to pH 6−7. The organic layer was washed with 5.0 mL of saturated $NaHCO_3$ and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography, eluting with 70% EtOAc/hexanes to yield 350 mg (65%) of acetate **39a** as a white foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.29 (m, 4H), 2.76 (s, 3H), 3.05 (m, 4H), 3.40 (q, 2H, J = 14.0 Hz), 3.58 (dd, 1H, J = 7.2, 14.1 Hz), 3.66 (dd, 1H, J = 5.2, 14.1 Hz), 4.09 (s, 3H), 6.40 (dd, 1H, J = 5.2, 6.8 Hz), 7.00 (d, 1H, J = 1.2 Hz), 7.28 (dd, 1H, J = 1.6, 8.4 Hz), 7.37 (dt, 1H, J = 1.2, 8.4 Hz), 7.63 (m, 2H), 7.74 (s, 1H), 7.82 (d, 1H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 34.4, 37.4, 45.7 52.2, 53.7, 61.5, 70.3, 124.0, 124.4, 124.87, 124.92, 127.1, 127.5, 128.0, 129.8, 131.7, 133.2, 134.7, 143.1, 146.0, 149.6, 158.9, 169.5; HRMS calcd for $C_{26}H_{30}N_4O_7S$ 543.1907 (M + H), found 543.1915 (M + H).

1-(2-Chloroquinolin-3-yl)-2-(5-{[4-(methylsulfonyl)piperazin-1-yl]methyl}-2-nitrophenyl)ethanone (37). To a solution of 550 mg (1.09 mmol) of alcohol **29** in 3 mL of isopropyl acetate was added 2.2 mL (31.0 mmol) of DMSO followed by 670 mg (6.54 mmol) of acetic anhydride. The reaction was stirred for 16 h at room temperature. To the reaction mixture was added 10 mL of saturated $NaHCO_3$ to adjust the pH to 8−9, followed by 10 mL of chloroform. The organic layer was washed with 40 mL of water and dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by silica chromatography, eluting with 70% EtOAc/hexane to afford 210 mg (38%) of **37** as a pale yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.61 (m, 4H), 2.82 (s, 3H), 3.29 (m, 4H), 3.67 (s, 2H), 4.80 (s, 2H), 7.45 (s, 1H), 7.50 (m, 1H), 7.67 (m, 1H), 7.87 (m, 1H), 7.96 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.4 Hz), 8.19 (m, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.4, 45.9, 48.5, 52.5, 61.5, 125.8, 126.3, 128.1, 128.5, 128.7, 129.0, 130.2, 132.5, 132.9, 134.2, 139.6, 145.0, 145.3, 147.5, 148.2, 196.9. Anal. Calcd for $C_{23}H_{23}ClN_4O_5S$: C, 54.92; H, 4.61; N, 11.14. Found: C, 54.64; H, 4.35; N, 10.56.

Preparation of 25 by Reductive Cyclization of Ketone 36. To a solution of 5.22 g (10.50 mmol) of ketone **30** in 60 mL of THF was added 2.10 g of Raney Nickel 2800 (H_2O). The reaction slurry was then heated to 65 °C for 7.5 h under 40 psi of H_2. The cooled reaction mixture was filtered over Celite and the solution concentrated under reduced pressure. The product was crystallized by addition of MeOH to the concentrated solution to yield 4.23 g (90%) of **25**, which was identical with that obtained above.

2-(2-Amino-5-{[4-methylsulfonyl)piperazin-1-yl]methyl}-phenyl)-1-(2-methoxyquinolin-3-yl)ethanol (40). To a solution of 1.00 g (2.00 mmol) of the alcohol **30** in 10 mL of THF was added 0.60 g of Ra/Ni 2800 (H_2O). The reaction mixture was heated at 65 °C for 6 h under 40 psi of H_2. The cooled reaction mixture was filtered over Celite and concentrated under reduced pressure, and the residue was purified over silica gel eluting with MeOH/$CHCl_3$ (5:95) to afforded 810 mg (86%) of the aniline alcohol **40** as a white foam: ^{1}H NMR

($CDCl_3$, 400 MHz) δ 2.41 (m, 4H), 2.75 (s, 3H), 2.83 (dd, 2H, J = 14.5, 8.4 Hz), 3.12 (m, 4H), 3.23 (dd, 1H, J = 14.5, 3.2 Hz), 3.37 (dd, 2H, J = 12.9, 16.6 Hz), 4.10 (br s, 2H), 4.18 (s, 3H), 5.27 (dd, 1H, J = 2.8, 8.4 Hz), 6.71 (d, 1H, J = 8.0 Hz), 6.87 (d, 1H, J = 1.6 Hz), 7.00 (dd, 1H, J = 2.0, 8.0 Hz), 7.40 (t, 1H, J = 6.8 Hz), 7.62 (ddd, 1H, J = 1.2, 7.2, 8.4 Hz), 7.71 (d, 1H, J = 8.0 Hz), 7.87 (d, 1H, J = 8.4 Hz), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.2, 39.9, 45.8, 52.1, 53.7, 62.2, 69.6, 116.2, 123.5, 124.4, 125.4, 127.0, 127.4, 127.5, 128.0, 128.9, 129.3, 132.5, 134.3, 144.6, 145.6, 159.2; HRMS calcd for $C_{24}H_{30}N_4O_4S$ 471.2060 (M + H), found 471.2071 (M + H).

Preparation of 2-(2-Amino-5-methylphenyl)-1-(2-methylquinolin-3-yl)ethanol (41). To a mixture of 13.0 g (58.3 mmol) of 3-trimethylsilylmethyl-4-nitrotoluene[52] and 10.9 g (58.0 mmol) of aldehyde **28** in 150 mL of isopropyl acetate was added 8.80 mL (8.80 mmol, 1 M solution) of TBAF in THF. The mixture was stirred at room temperature for 30 min and quenched with 60 mL of saturated NH_4Cl. The layers were separated and the organic layer was washed with 60 mL of water and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified over silica gel to give 12.0 g (74%) of 1-(2-methoxyquinolin-3-yl)-2-(5-methyl-2-nitrophenyl)ethanol, which was used in the next step directly.

To a solution of 600 mg (1.78 mmol) of the above alcohol in 8.0 mL of THF was added 360 mg of Ra/Ni 2800 (H_2O). The reaction mixture was heated at 65 °C for 6 h under 40 psi of H_2. The cooled reaction mixture was filtered over Celite and concentrated under reduced pressure, and the residue was purified over silica gel eluting with MeOH/$CHCl_3$ (5:95) to afforded 320 mg (58%) of the aniline alcohol **41** as a white solid: mp 139−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 2.71 (dd, 1H, J = 9.6, 14.1 Hz), 2.83 (br s, 1H), 3.17 (dd, 1H, J = 2.4, 14.1 Hz), 3.92 (br s, 2H), 4.18 (s, 3H), 5.22 (dd, 1H, J = 1.6, 9.6 Hz), 6.67 (d, 1H, J = 7.6 Hz), 6.91 (s, 1H), 6.92 (d, 1H, J = 7.6 Hz), 7.40 (ddd, 1H J = 1.2, 6.8, 8.0 Hz), 7.62 (ddd, 1H, J = 1.6, 6.8, 8.4 Hz), 7.75 (dd, 1H, J = 0.8, 8.0 Hz), 7.88 (d, 1H, J = 8.0 Hz), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 40.3, 53.6, 59.6, 116.5, 123.9, 124.3, 125.5, 126.9, 127.6, 128.2, 128.3, 128.6, 129.2, 131.9, 134.1, 142.6, 145.7, 159.2. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N 9.08. Found: C, 73.62; H, 6.60; N, 8.86.

Preparation of 2-Methoxy-3-(5-methyl-1*H*-indol-2-yl)-quinoline (42). To a solution of 3.50 g (10.0 mmol) of 1-(2-methoxyquinolin-3-yl)-2-(5-methyl-2-nitrophenyl)ethanol in 20 mL of isopropyl acetate was added 9.70 g (120 mmol) of DMSO followed by 6.38 g (62.0 mmol) of acetic anhydride. The mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$. The organic layer was washed with saturated $NaHCO_3$ (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was concentrated and the solid slurried in MTBE and filtered to afford 2.40 g (69%) of 1-(2-methoxyquinolin-3-yl)-2-(5-methyl-2-nitrophenyl)ethanone as a solid: mp 173.3−175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 4.22 (s, 3H), 4.77 (s, 2H), 7.21 (s, 1H), 7.26 (dd, 1H, J = 1.2, 8.4 Hz), 7.43 (ddd, 1H, J = 1.2, 6.8, 8.0 Hz), 7.72 (ddd, 1H, J = 1.6, 6.8, 8.4 Hz), 7.84 (dd, 1H, J = 1.2, 8.0 Hz), 7.88 (d, 1H, J = 8.4 Hz), 8.1 (d, 1H, J = 8.4 Hz), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 48.9, 53.9, 123.3, 124.6, 124.9, 125.5, 127.1, 128.9, 129.2, 131.2, 131.9, 134.5, 141.5, 141.8, 144.8, 148.0, 159.2, 196.3. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.69; H, 4.58; N, 8.33.

To a solution of 1.00 g (2.97 mmol) of the above ketone in 20 mL of THF was added 600 mg of Raney Nickel 2800 (H_2O). The reaction slurry was then heated to 65 °C for 7.5 h under 40 psi of H_2. The cooled reaction mixture was filtered over Celite and the solution concentrated under reduced pressure. The product was purified by silica gel chromatography to give 650 mg (76%) of **42** as a yellow solid: mp 139.5−141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (s, 3H), 4.3 (s, 3H), 7.02 (d, 1H, J = 2.0 Hz), 7.07 (dd, 1H, J = 1.6, 8.4 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.43 (ddd, 1H J = 1.2, 6.8, 8.0 Hz), 7.63 (ddd, 1H, J = 1.6, 6.8, 8.4 Hz), 7.79 (dd, 1H, J = 0.8, 8.0 Hz), 7.89 (d, 1H, J = 8.0 Hz), 8.46 (s, 1H), 9.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 48.9, 53.9, 123.3, 124.6, 124.9, 125.5, 127.1, 128.9, 129.2, 131.2, 131.9, 134.5, 141.5, 141.8, 144.8, 148.0, 159.2, 196.3. Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 78.88; H, 5.47; N, 9.61.

2-Chloro-3-[5-[[4-(methysulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline (43). To a solution of 75 mg (0.149 mmol) of **37** in 1 mL of THF was added 50 mg of Raney Nickel 2800 (55 wt % of slurry in EtOH). The mixture was stirred at room temperature for 20 h under 40 psi of H_2. The reaction was filtered through a 0.45 μm syringe filter and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 29.1 mg (46%) of **43** as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.62 (m, 4H), 2.79 (s, 3H), 3.27 (m, 4H), 3.68 (s, 2H), 6.98 (s, 1H), 7.25 (d, 1H, J = 8.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.62 (m, 2H), 7.78 (t, 1H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.4 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.42 (s, 1H), 8.86 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 45.8, 52.1, 63.0, 104.7, 111.1, 121.4, 124.7, 125.8, 127.0, 127.5, 127.6, 128.1, 128.3, 130.8, 133.4, 136.2, 138.3, 146.6, 147.6, 158.2. Anal. Calcd for $C_{23}H_{23}ClN_4O_2S$: C, 60.72; H, 5.10; N, 12.31. Found: C, 60.45; H, 5.12; N, 12.11.

The second product to elute from the column (14.4 mg, 23%) was identified as 3-[5-[[4-(methysulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline (**44**), which was obtained as a yellow-green solid: mp 211−212 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.46 (m, 4H), 2.84 (s, 3H), 3.08 (m, 4H), 3.56 (s, 2H), 7.09 (d, 1H, J = 8.3 Hz), 7.14 (s, 1H), 7.38 (d, 1H, J = 8.3 Hz), 7.47 (s, 1H), 7.62 (t, 1H, J = 7.7 Hz), 7.71 (t, 1H, J = 7.7 Hz), 7.95 (d, 1H, J = 8.3 Hz), 8.00 (d, 1H, J = 8.3 Hz), 11.77 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 34.2, 46.0, 52.2, 62.7, 100.9, 111.7, 121.2, 124.4, 126.0, 127.8, 128.1, 128.6, 129.0, 129.4, 129.8, 130.2, 137.4, 147.1, 149.0. Anal. Calcd for $C_{23}H_{24}N_4O_2S\cdot H_2O$: C, 62.99; H, 5.98; N, 12.78. Found: C, 63.02; H, 5.62; N, 12.47.

***trans*-3-{2-[5-(4-Methanesulfonylpiperazine-1-ylmethyl)-2-nitrophenyl]vinyl}-2-methoxyquinoline (45). Method A:** To a solution of 3.50 g (7.00 mmol) of alcohol **30** in 50 mL of isopropyl acetate was added 1.76 g (8.40 mmol) of TFAA. After the solution was stirred for 30 min at room temperature, 1.39 g (9.10 mmol) of DBU was added and the mixture was heated to 60 °C for 30 min. The reaction mixture was cooled to room temperature and diluted with 20 mL of brine, and the layers were separated. The organic layer was washed with 25 mL of water and concentrated under reduced pressure. The crude residue was slurried in MTBE to give 2.71 g (80%) of **45** as a yellow solid: mp 156−157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.63 (m, 4H), 2.81 (s, 3H), 3.31 (m, 4H), 3.67 (s, 2H), 4.18 (s, 3H), 7.42 (m, 3H), 7.63 (dt, 1H, J = 6.9 and 1.4 Hz), 7.83 (m, 4H), 7.98 (d, 1H, J = 8.4 Hz), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.5, 45.9, 52.5, 53.8, 61.8, 121.8, 124.6, 125.2, 125.4, 126.4, 127.0, 127.8, 127.9, 128.5, 128.6, 129.9, 133.4, 135.1, 143.9, 146.3, 147.1, 159.8. Anal. Calcd for $C_{24}H_{26}N_4O_5S$: C, 59.74; H, 5.43; H, 11.61. Found: C, 59.51; H, 5.17; N, 11.53.

Method B: To a solution of 1.00 g (2.87 mmol) of **21** in 10 mL of DMF was added 532 mg (2.87 mmol) of **46**, 19.3 mg (0.086 mmol) of $Pd(OAc)_2$, and 87.4 mg (0.287 mmol) of P(*o*-tolyl)$_3$. The solution was degassed by bubbling nitrogen through the solution for 30 min. To the mixture was added 436 mg (4.31 mmol) of NEt_3 and the mixture was heated to 100 °C in a sealed tube for 4 h. The reaction mixture was cooled to room temperature and diluted with 50 mL of EtOAc and 50 mL of water. The layers were separated and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel chro-

(52) Bartoli, G.; Palmieri, G.; Petrini, M.; Bosco, M.; Dalpozzo, R. *Tetrahedron* **1990**, *46*, 1379.

matography to give 873 mg (63%) of **45**, which was identical with that prepared by Method A.

Preparation of 2-Methoxy-3-vinylquinoline (46). To a solution of 5.90 g (16.4 mmol) of methyltriphenylphosphonium bromide in 30 mL of THF was added 10.3 mL (16.4 mmol) of a 1.6 M solution of *n*-BuLi and the resulting mixture was stirred at room temperature for 30 min. To the solution was added dropwise 3.00 g (14.9 mmol) of aldehyde **28** in 30 mL of THF and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was filtered to remove insoluble salts and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 2.40 g (81%) of **46** as a yellow oil, which was used immediately in the next reaction: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.13 (s, 3H), 5.43 (d, 1H, J = 10.6 Hz), 5.94 (d, 1H, J = 17.0 Hz), 7.00 (dd, 1H, J = 17.7 and 11.2 Hz), 7.36 (t, 1H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.1 Hz), 7.72 (d, 1H, J = 7.9 Hz), 7.83 (d, 1H, J 8.4 Hz), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.7, 117.2, 123.0, 124.2, 125.5, 127.0, 127.5, 129.3, 131.3, 134.3, 146.0, 160.0. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.47; H, 5.61; N, 7.34.

Preparation of *cis*-3-{2-[5-(4-Methanesulfonylpiperazine-1-ylmethyl)-2-nitrophenyl]vinyl}-2-methoxyquinoline (47) by Photolysis of 45. A solution of 1.0 g (2.10 mmol) of **45** in 10 mL of DMF was irradiated at 300 nm for 16 h. The reaction mixture was concentrated in vacuo to a yellow oil. A yellow solid crystallized upon standing. The oily solid was diluted with EtOAc (5 mL) and filtered by washing with EtOAc. The filtrate was concentrated to an oil, from which a solid crystallized upon standing. The oily solid was diluted with EtOAc (5 mL) and filtered. The filtrate was concentrated in vacuo to afford 400 mg (40%) of pure **47** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (m, 4H), 2.54 (m, 4H), 2.63 (s, 3H), 3.32 (s, 2H), 4.05 (s, 3H), 6.92 (d, 1H, J = 12.0 Hz), 7.15 (d, 1H, J = 12.0 Hz), 7.20 (s, 1H), 7.30 (m, 2H), 7.36 (d, 1H, J = 8.0 Hz), 7.47 (s, 1H), 7.60 (m, 1H), 7.78 (d, 1H, J = 8.3 Hz), 8.12 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.6, 45.2, 51.8, 53.7, 61.1, 121.0, 124.4, 124.6, 125.0, 126.0, 126.9, 127.1, 128.4, 129.6, 129.8, 131.9, 133.7, 138.0, 144.0, 145.8, 147.0, 160.1.

Preparation of *trans*-3-{2-[5-(4-Methanesulfonylpiperazine-1-ylmethyl)-2-nitrophenyl]vinyl}quinoline (50). To a mixture of 1.87 g (4.85 mmol) of **26** and 762 mg (4.85 mmol) of aldehyde **49** in 25 mL of isopropyl acetate was added dropwise 1.00 mL (1.00 mmol) of a 1 M solution of TBAF. After 30 min, the reaction mixture was diluted with 15 mL of isopropyl acetate and washed with 30 mL of saturated NH_4Cl and 30 mL of water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 1.84 g (81%) of the alcohol, which was used in the next step without further purification.

To a solution of 1.59 g (3.38 mmol) of the above alcohol in 45 mL of isopropyl acetate was added 852 mg (4.06 mmol) of TFAA. After the solution was stirred for 30 min at room temperature, 772 mg (5.07 mmol) of DBU was added and the mixture was heated to 60 °C for 30 min. The reaction mixture was cooled to room temperature and diluted with 20 mL of brine, and the layers were separated. The organic layer was washed with 25 mL of water and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give 1.10 g (72%) of **50** as a yellow solid: mp 211−212 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.86 (s, 3H), 2.91 (m, 4H), 3.48 (m, 4H), 3.94 (s, 2H), 7.32 (s, 1H), 7.48 (d, 1H, J = 7.3 Hz), 7.71 (t, 1H, J = 7.3 Hz), 7.87 (m, 3H), 7.98 (d, 1H, J = 8.4 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.28 (d, 1H, J = 8.4 Hz), 8.52 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.4, 42.6, 50.0, 58.1, 123.6, 124.0, 125.9, 126.4, 126.9, 128.1, 128.4, 128.6, 128.8, 128.9, 130.8, 132.3, 145.4, 146.1, 147.6. Anal. Calcd for $C_{23}H_{24}N_4O_4S$: C, 61.05; H, 5.35; N, 12.38. Found: C, 61.32; H, 5.33; N, 12.02.

Preparation of *trans*-3-{2-[5-(4-Methanesulfonylpiperazine-1-ylmethyl)-2-nitrophenyl]vinyl}-2-chloroquinoline (51). To a solution of 1.00 g (1.98 mmol) of **29** in 25 mL of isopropyl acetate was added 500 mg (2.38 mmol) of TFAA. After the solution was stirred for 30 min at room temperature, 904 mg (5.94 mmol) of DBU was added and the mixture was heated to 60 °C for 30 min. The reaction mixture was cooled to room temperature and diluted with 30 mL of brine, and the layers were separated. The organic layer was washed with 35 mL of water and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give 800 mg (83%) of **51** as a yellow solid: mp 199−200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64 (m, 4H), 2.82 (s, 3H), 3.31 (m, 4H), 3.70 (s, 2H), 7.45 (s, 1H), 7.50 (d, 1H, J = 15.9 Hz), 7.60 (m, 1H), 7.77 (m, 3H), 7.90 (d, 1H, J = 8.2 Hz), 8.02 (d, 1H, J = 5.0 Hz), 8.04 (d, 1H, J = 5.0 Hz), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.4, 46.0, 52.5, 61.7, 125.3, 127.5, 127.7, 127.9, 128.4, 128.5, 128.6, 129.0, 129.4, 132.7, 135.0, 144.5, 147.0, 147.3, 149.9. Anal. Calcd for $C_{23}H_{23}ClN_4O_4S$: C, 56.73; H, 4.76; N, 11.51. Found: C, 56.55; H, 4.48; N, 11.34.

Preparation of 25 by Palladium-Catalyzed Reductive Cyclization of 45. Method A. In an autoclave was added sequentially 45.0 g (93.3 mmol) of **45**, 210 mg (0.935 mmol) of $Pd(OAc)_2$, 336 mg (0.187 mmol) of 1,10-phenanthroline, and 1.3 L of DMF. The vessel was purged three times successively with N_2 and CO and then pressurized to 15 psig of CO and stirred at 70 °C for 14 h. The reaction mixture was cooled to room temperature, filtered over a pad of solka floc (filter aid), and concentrated to a final volume of 150 mL. The resulting solution was heated to 50 °C and 50 mL of MeOH was added. Upon cooling the product crystallized and was collected by filtration to afford 39.4 g (94%) of **25**, which was identical with that isolated from the reductive cyclization of ketone **37**.

Method B: In an autoclave was added sequentially 4.00 g (8.30 mmol) of **45**, 112 mg (0.500 mmol) of $Pd(OAc)_2$, 520 mg (2.00 mmol) of PPh_3, and 40 mL of MeCN. The vessel was purged three times successively with N_2 and CO and then pressurized to 60 psig of CO and stirred at 70 °C for 15 h. The reaction mixture was filtered while hot through a sintered glass frit that removed the insoluble indole dimer **48**. The filtrate was concentrated in vacuo to provide 3.55 g (95%) of **25**, which was identical with that isolated from the reductive cyclization of ketone **37**. The indole dimer **48** (2,2′-bis(2-methoxyquinolin-3-yl)-5,5′-bis{[4-(methylsulfonyl)piperazin-1-yl]methyl}-1*H*,1′*H*-3−3′-biindole) was isolated as a light yellow solid: mp 324−326 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.15 (m, 4H), 2.22 (m, 4H), 2.82 (s, 6H), 2.92 (m, 8H), 3.22 (d, 2H, J = 12.4 Hz), 3.44 (d, 2H, J = 12.4 Hz), 3.67 (s, 6H), 7.01 (m, 4H), 7.29 (dt, 2H, J = 7.9 and 0.8 Hz), 7.37 (d, 2H, J = 8.3 Hz), 7.50 (d, 2H, J = 7.9 Hz), 7.57 (dt, 2H, J = 7.0 and 1.2 Hz), 7.67 (d, 2H, J = 8.3 Hz), 7.96 (s, 2H), 11.3 (br s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.8, 45.1, 51.3, 52.8, 62.4, 108.2, 110.9, 118.2, 120.2, 123.1, 124.3, 126.1, 126.9, 127.3, 129.3, 130.2, 135.6, 138.4, 144.8,159.0; HRMS calcd for $C_{48}H_{51}N_8O_6S_2$ 899.3373 (M + H), found 899.3372 (M + H).

General Procedure for the Reductive Cyclization of Nitrostyrenes with P(OEt)$_3$. A solution of 1.00 mmol of the appropriate nitrostyrene in 5 mL of $P(OEt)_3$ was heated to 155 °C for 2 h and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography to give the product.

Preparation of 25 by Reductive Cyclization of 45 with P(OEt)$_3$. According to the general procedure, reaction of 1.50 g (3.10 mmol) of **45** with 15.5 mL of $P(OEt)_3$ afforded 908 mg (62%) of **25**, which was identical with that isolated from the reductive cyclization of ketone **36**.

Preparation of 43 by Reductive Cyclization of 51 with P(OEt)$_3$. According to the general procedure, reaction of 1.06 g (2.18 mmol) of **51** in 11 mL of $P(OEt)_3$ gave 600 mg (61%) of **43**, which was identical with that isolated from the reductive cyclization of ketone **37**.

Preparation of 44 by Reductive Cyclization of 50 with P(OEt)$_3$. According to the general procedure, reaction of 700 mg (1.55 mmol) of **50** in 7.5 mL of $P(OEt)_3$ gave 468 mg (72%)

of **44**, which was identical with that isolated from the reductive cyclization of ketone **37**.

Preparation of 3-(5-{[4-(Methanesulfonyl)-1-piperazinyl]methyl}-1*H*-indol-2-yl)quinolin-2(1*H*)one Hydrochloride (1). To a stirred solution of 10.2 g (22.6 mmol) of **25** in 100 mL of DMF at 70 °C was added 11.2 mL (135.8 mmol) of concentrated HCl. The resulting slurry was stirred at 70 °C for 2 h. To the slurry was added dropwise 300 mL of 2-propanol and the mixture was allowed to cool to room temperature and the solid collected by filtration. The wet filter cake was washed with 25 mL of 2-propanol and dried at 40 °C under vacuum/nitrogen sweep for 12 h to give 10.7 g (100%) of **1** as a mono HCl salt and a yellow solid: mp 250 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.98 (s, 3H), 3.12 (m, 2H), 3.33 (t, 2H, J = 12.6 Hz), 3.39 (m, 2H), 3.70 (d, 2H, J = 12.6 Hz), 4.42 (m, 2H), 7.25 (m, 1H), 7.39 (m, 2H), 7.41 (d, 1H, J = 8.2 Hz), 7.52 (ddd, 1H, J = 8.2, 7.2, and 1.2 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 7.7 Hz), 7.82 (s, 1H), 8.63 (s, 1H), 11.45 (br s, 1H), 11.86 (s, 1H), 12.21 (s, 1H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 35.2, 42.2, 49.7, 53.4, 102.2, 112.0, 115.0, 119.3, 119.9, 122.1, 122.3, 123.7, 124.9, 127.8, 130.3, 134.6, 134.8, 136.8, 137.7, 160.5. Anal. Calcd for $C_{23}H_{24}N_4O_3S$·HCl: C, 58.40; H, 5.33; N, 11.85. Found: C, 58.38; H, 5.26; N, 11.71.

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Supporting Information Available: Spectroscopic data for compounds **38**–**40**, **47**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org. This material is available free of charge via the Internet at http://pubs.acs.org.

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