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Efficient Syntheses of KDR Kinase Inhibitors Using a Pd-Catalyzed Tandem C−N/Suzuki Coupling as the Key Step

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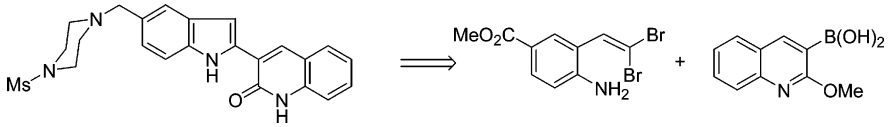

A family of four potent KDR kinase inhibitors containing an indol-2-yl quinolin-2-one structure was utilizing a Pd-catalyzed tandem C−N and C−C coupling sequence.

Introduction

Protein tyrosine kinases are an important family of enzymes that catalyze phosphorylation of the OH group on selected tryrosine residues using ATP. These enzymes are involved in many important biological processes such as cellular signaling pathways, regulation of key cell function, proliferation, differentiation, anti-apoptotic signaling, and neutrile growth.[1] Dysregulation of enzymes under pathological settings are responsible for many diseases such as cancer, tumor growth, pathological angiogenesis, and diabetes.[2] KDR (kinase insert domain-containing receptor) is one of the human tyrosine kinases that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor-induced angiogenesis.[3] Therefore, compounds which inhibit or regulate the KDR kinase are of great interest as potential therapeutic agents.

Most small molecule inhibitors bind to the active side of tyrosine kinases via two key hydrogen bonds and other secondary interactions by mimicking the adenine moiety of the natural ligand ATP.[4] Indoles[5] are widely found in medicinal agents and are considered "privileged scaffolds". SUGEN (now part of Pfizer) found an indolin-2-one as a pharmacophore for potent KDR kinase inhibitors,[6] and Merck recently reported a class of potent KDR kinase inhibitors containing the indol-2-yl quinolin-2-one structure (Figure 1).[7] The inhibitors disclosed by Merck differ in the substitution at the 5-position of the indole ring (Figure 2). Compounds **2**−**4** have an O-linker between the indole and the side chain, while compound **1** has a methylene-linked piperazine moiety.

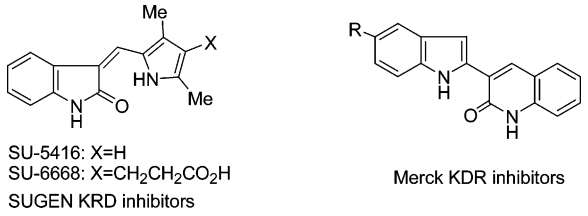

FIGURE 1. Indole-containing KRD kinase inhibitors.

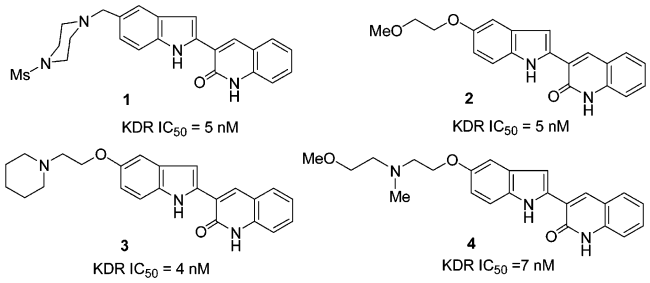

FIGURE 2. Merck's family of KDR kinase inhibitors.

Compound **1** has been advanced to clinical development for cancer therapy; therefore, large quantities of the drug candidate are required via chemical synthesis.[7] Many different literature

(1) Krause, D. S.; Van Ettern, R. A. *N. Engl. J. Med.* **2005**, *353*, 172.
(2) (a) Zetter, B. R. *Annu. Rev. Med.* **1998**, *49*, 407. (b) Traxler, P. *Expert Opin. Ther. Targets* **2003**, *7*, 215. (c) Glade-Bender, J.; Kandel, J. J.; Yamashiro, D. J. *Expert Opin. Biol. Ther.* **2003**, *3*, 263.
(3) (a) Yancopoulos, G. D.; Davis, S.; Gale, N. W.; Rudge, J. S.; Wiegand, S. J.; Holash, J. *Nature* **2000**, *407*, 242. (b) Carmeliet, P.; Jain, R. K. *Nature* **2000**, *407*, 249.
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(5) (a) Sundberg, R. J., Ed. *Indoles*; Academic Press: San Diego, 1996. (b) Gribble, G. W. *Perkin 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
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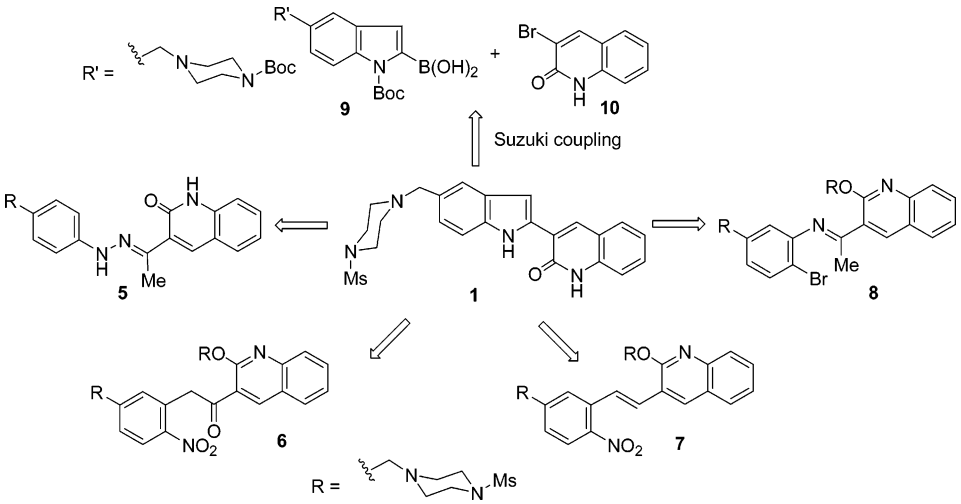
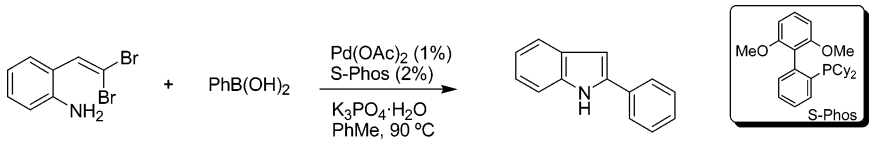
SCHEME 1. Merck's Process Routes toward KDR Inhibitor 1



SCHEME 2. Novel Indole Synthesis via a Pd-Catalyzed Tandem C−N/Suzuki Coupling



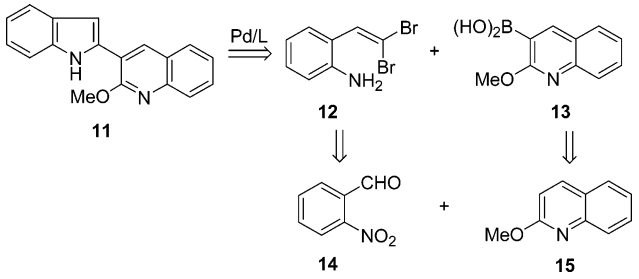
methods (Scheme 1) have been used for the synthesis of **1**, including: (1) a Fisher indole reaction from hydrazone **5**, (2) reductive condensation of nitroketone **6**, (3) nitrene C−H insertion cyclization via reduction of **7**, (4) Pd-catalyzed cyclization of imime **8**, and (5) Suzuki coupling of boronic acid **9** and aryl bromide **10**. Among these methods, reductive cyclization from either **6** or **7** have been the most efficient routes from readily available starting materials. The convergent Suzuki coupling between **9** and **10** also proved to be successful for the preparation of kilogram quantities of product **1**. The overall yields range from 50 to 60% over six to seven steps.

Recently, we have developed a new general and efficient route to indoles via a Pd- or Cu-catalyzed tandem cross-coupling using a *gem*-dihalovinylaniline.[8] In particular, Pd-catalyzed tandem C−N and Suzuki coupling allows for the formation of a large range of 2-substituted indoles from a *gem*-dihalovinylaniline and commercially available boronic acids (Scheme 2).[8a] Here, we report the syntheses of KDR inhibitors **1**−**4** to highlight our methodology and its generality and efficiency.

Results and Discussion

The retrosynthetic plan is straightforward for the construction of the indole−quinolinone core (Scheme 3). A tandem coupling *gem*-dibromovinylaniline **12** and 2-methoxyquinolin-3-ylboronic acid (**13**) would give the indole−methoxyquinoline **11**, which

SCHEME 3. Key Retrosynthetic Step for the Core of Merck's KDR Inhibitors



is known to readily hydrolyze upon treatment with strong acid to give the indole−quinolinone core.[7a] We have developed efficient protocols for the synthesis of **12** from corresponding nitrobenzaldehyde **14**. Boronic acid **13** could be obtained from directed ortholithiation of 2-methoxyquinoline (**15**). A model reaction between substrate **12** and boronic acid **13** using a catalytic amount of $Pd(OAc)_2$ (3 mol %) and S-Phos (6 mol %) in the presence of $K_3PO_4 \cdot H_2O$ in toluene at 100 °C gave the desired product **11** in 75% yield.

Initially, a one-pot, two-step procedure through *gem*-dibromoolefination[9] followed by Sn(II) reduction was used for the synthesis of *gem*-dibromovinyl substrate **18** from nitrobenzaldehyde **16** in good yield (Scheme 4).[8a] However, considering $SnCl_2 \cdot H_2O$ as a reductant generates large amounts of waste (six electrons requires a minimum of 3 equiv of this reagent), we sought a better method for reduction such as catalytic hydrogenation. The presence of an alkene and two halogens poses a

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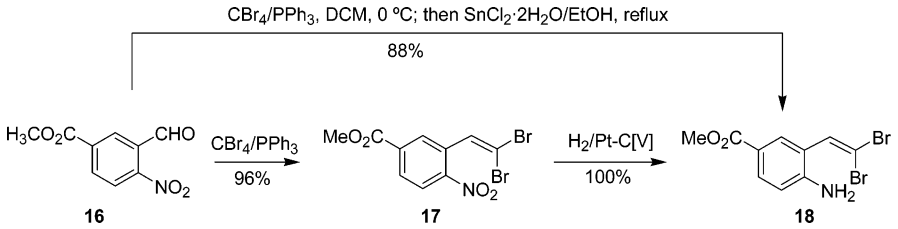
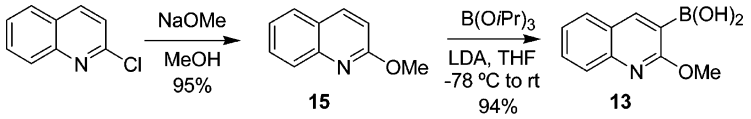
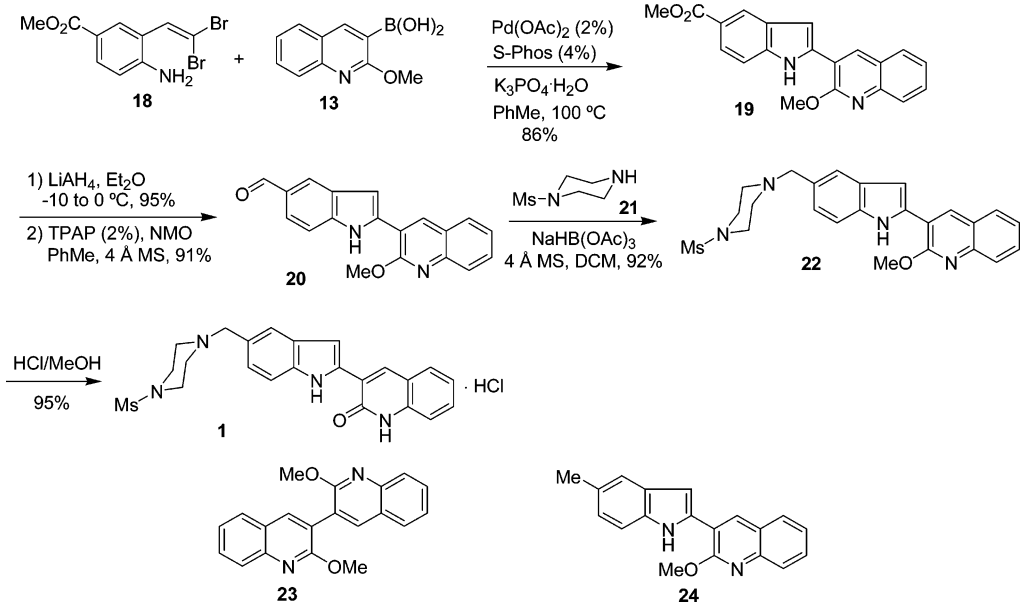
SCHEME 4



SCHEME 5



SCHEME 6. Synthesis of KDR Kinase Inhibitor 1



significant challenge for the selective reduction. While most traditional heterogeneous catalysts such as Pd/C were inefficient, 1% vanadium-doped platinum on carbon (abbreviated as 1% Pd−C[V], supplied by Degussa) proved to be extremely selective.[10] A two-step procedure using Ramirez olefination[9a] with CBr_4/PPh_3 led to efficient formation of the *gem*-dibromoolefin **17**, which upon catalytic hydrogenation using 1% Pt−C[V] catalyst gave the aniline substrate **18** in quantitative yield.

The synthesis of the quinoline boronic acid **13** started from commercially available 2-chloroquinoline, which reacted with sodium methoxide in methanol to give the desired 2-methoxyquinoline (**15**) in excellent yield.[11] Upon treatment of **15** with LDA in the presence of triisopropyl borate in THF, boronic acid **13** was obtained in excellent yield as a white crystalline solid (Scheme 5).

The Pd-catalyzed tandem C−N/C−C coupling of **18** with **13** proceeded smoothly in the presence of $K_3PO_4 \cdot H_2O$ in 86% yield (Scheme 6). Excess **13** (1.5 equiv) was required to compensate for a parasitic processes such as protodeboration leading to **15** and homocoupling product leading to diquinoline **23** under these conditions. When a gram-scale coupling was performed, the solid product **19** was obtained by recrystallization, although the yield was slightly lower (80%).

Reduction of the ester **19** using $LiAH_4$ at −10 °C gave the desired benzyl alcohol in good yield. Low temperature was required to prevent formation of the over-reduced product **24**. TPAP/NMO[12] was found to be the optimal oxidant to convert the benzyl alcohol into aldehyde **20** using only 2 mol % catalyst loading. A reductive amination of the aldehyde **20** and *N*-mesylpiperizine (**21**) successfully afforded the benzylpiperizine **22**. The KDR kinase inhibitor **1** was obtained as its hydrochloride salt in excellent yield under hydrolytic conditions.

Our indole synthesis approach was also successfully applied to the remaining KDR inhibitors (**2**−**4**) starting from commercially available 5-hydroxy-2-nitrobenzaldehyde (**25)** (Scheme 7). Alkylation of phenol **25** with either 2-methoxyethyl iodide (**27a**) or *N*-2-chloroethylpiperidine hydrochloride (**27b**) in the presence of K_2CO_3 in DMF afforded products **26a** or **26b** in good yield. Alkylation with alkyl chloride **27c**, however, was less efficient. Subjecting aldehydes **26 (a** or **b** or **c**) to the Ramirez olefination, followed by catalytic hydrogenation using 1% Pd−C[V] gave aniline substrates **29 (a** or **b** or **c**) in good

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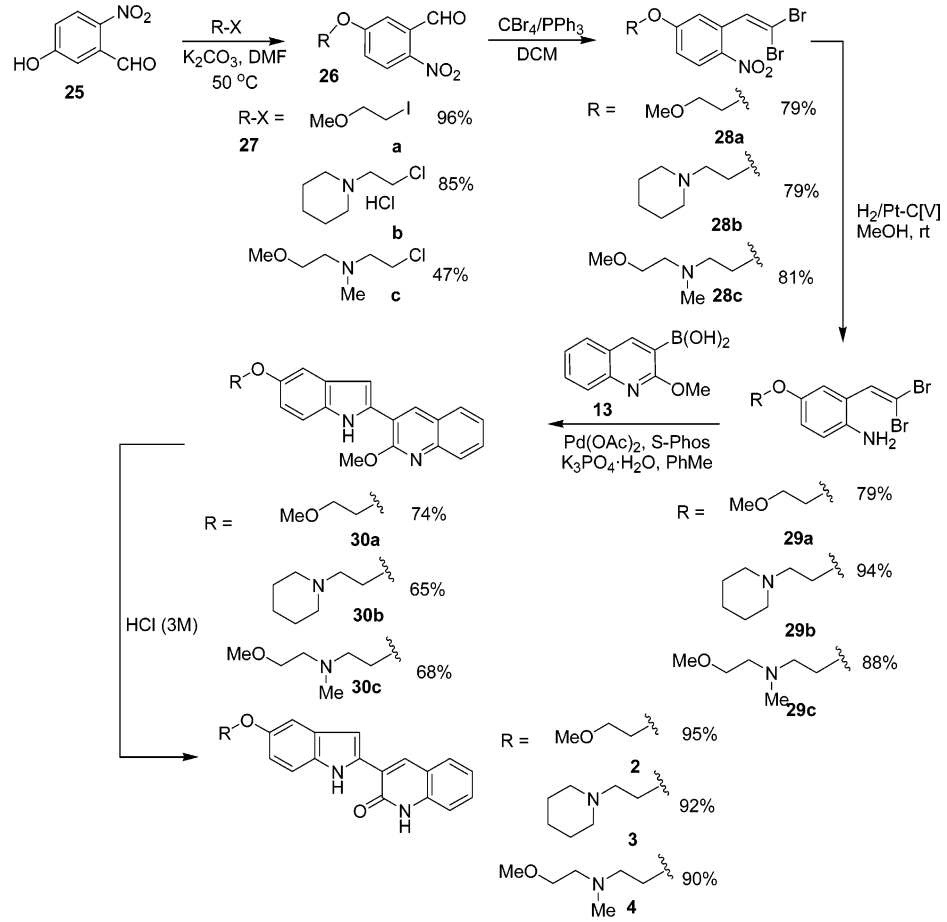
SCHEME 7



yield. The tandem coupling reactions using *gem*-dibromovinylaniline substrates **29 (a or b** or **c**) with boronic acid **13** furnished the indole **30** (**a** or **b** or **c**), albeit in lower yield than **19**. Upon hydrolysis, the desired KDR inhibitors **2**−**4** were obtained in excellent yields.

In summary, we have successfully demonstrated our newly developed indole synthesis methodology in the preparation of a family of KDR kinase inhibitors, which have potential use in cancer therapy. KDR kinase inhibitor **1** was obtained in an overall 63% yield in seven linear steps, while KDR inhibitors **2**−**4** were obtained in an overall yield of 20−42% over five steps. This method is readily adapted to synthesize many more analogues of KDR kinase inhibitors.

Experimental Section

Preparation of Methyl 3-(2,2-dibromovinyl)-4-nitrobenzoate (17). To a solution of methyl 3-formyl-4-nitrobenzoate (3.14 g, 15 mmol) and CBr_4 (5.48 g, 16.5 mmol) in DCM (50 mL) was added dropwise PPh_3 (7.86 g, 30 mmol) solution in DCM (50 mL) at 0 °C. After addition, the mixture was stirred for 1 h and warmed to rt. The solution was filtered through a short silica gel column, eluting with 20% EtOAc/hexanes. The solvent was evaporated, and the residue was purified by chromatography with 10−20% EtOAc/hexanes to afford the product as a slightly yellow solid (5.23 g, 95.5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, t, J = 0.8 Hz), 8.19−8.13 (2H, m), 7.76 (1H, s), 3.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.4, 134.7, 133.2, 133.1, 131.7, 130.6, 125.2, 94.9, 53.2; HRMS (EI) calcd for $C_{10}H_8NO_4Br_2$ ($[M]^+$) 363.8820, found 363.8823.

Methyl 4-Amino-3-(2,2-dibromovinyl)benzoate (18). A mixture of methyl 3-(2,2-dibromovinyl)-4-nitrobenzoate (3.65 g, 10 mml) and 1% Pt−C[V] (365 mg) in MeOH (30 mL) was hydrogenated under 1 atm of H_2 (balloon) for 8 h until all the starting material was consumed. The catalyst was removed by filtration, and the solvent was removed under vacuum to afford the product as an analytically pure sample without chromatographic purification (3.35 g, 100%). ^{1}H NMR was identical to the one-pot procedure using $SnCl_2 \cdot 2H_2O$ as the reducing agent: R_f = 0.20 (20% EtOAc in hexanes); mp 112−113 °C; IR (neat, cm^{-1}) 3476, 3368, 3244, 2950, 1698, 1623, 1502, 1437, 1289, 1243, 1198, 1149, 1106. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, J = 1.8 Hz), 7.84 (1H, dd, J = 8.5, 1.9 Hz), 7.29 (1H, s), 6.98 (1H, d, J = 8.4 Hz), 4.14 (2H, br), 3.86 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 147.9, 133.2, 131.8, 131.7, 120.8, 120.0, 114.9, 94.8, 52.0; HRMS (EI) calcd for $C_{10}H_9NO_2Br_2$ ($[M]^+$) 332.9000, found 332.9004.

2-Methoxy-3-quinolin-3-ylboronic Acid (13). To a solution of 2-methoxyquinoline[11] (10.0 g, 62.8 mmol) and triisopropyl borate (17.86 g, 95.1 mmol) in THF (140 mL) at −78 °C was added a solution of LDA (75.4 mmol, prepared from *i*-Pr_2NH and *n*-BuLi). The mixture was stirred at −78 °C for 4 h and slowly warmed to rt overnight. The reaction was quenched with saturated NH_4Cl (68 mL) and acidified to pH = 5 with 3 M HCl. Organic solvents (THF and hexanes) were evaporated under vacuum, and boronic acid was precipitated as a white solid. The resulting mixture was filtered through a Buchner funnel, and the solid was washed thoroughly with H_2O to afford the boronic acid **13** after dried under high vacuum (12.11 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (1H, s), 7.85 (1H, d, J = 8.3 Hz), 7.80 (1H, d J = 7.9 Hz), 7.68 (1H, dd, J = 14.1, 1.1 Hz), 7.41 (1H, J = 7.5 Hz), 5.91 (2H, s, br), 4.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.8, 148.1, 131.1, 128.6, 127.4, 125.5, 124.7, 53.9; HRMS (EI) calcd for $C_{10}H_{10}BNO_3$ ($[M]^+$) 203.0754, found 203.0758.

Methyl 2-(2-Methoxyquinolin-3-yl)-1*H*-indole-5-carboxylate (19). To a 5 mL round-bottomed flask was charged **18** (0.1675 g,

0.5 mmol), **13** (0.1523 g, 0.75 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), S-Phos (12.3 mg, 0.03 mmol), and $K_3PO_4 \cdot H_2O$ (0.58 g, 2.5 mmol). The solid mixture was purged with argon for 10 min followed by addition of toluene (2.5 mL). The resulting mixture was stirred at rt for 2 min and heated at 100 °C for 1.5 h. The mixture was diluted with EtOAc (10 mL) and H_2O, and the organic phase was separated and dried over Na_2SO_4. The crude material was chromatographed with 20% EtOAc/hexanes to afford the product as a white solid (0.143 g, 86%): ^{1}H NMR (300 MHz, DMSO) δ 11.89 (1H, s), 8.74 (1H, s), 8.31 (1H, s), 7.94 (1H, d, J = 7.2 Hz), 7.84 − 7.77 (2H, m), 7.70 (1H, dd, J = 7.0, 1.3 Hz), 7.56 (1H, d, J = 8.5 Hz), 7.50 (1H, dd, J = 6.9, 1.2 Hz), 7.32 (1H, d, J = 1.3 Hz), 4.18 (3H, s), 3.86 (3H, s); ^{13}C NMR (100 MHz, DMSO) δ 167.2, 158.3, 144.7, 139.4, 135.5, 134.2, 130.0, 127.8, 127.7, 126.4, 124.9, 124.8, 123.0, 122.9, 120.9, 116.5, 111.4, 104.7, 53.8, 51.7; HRMS (EI) calcd for $C_{20}H_{16}N_2O_3$ ([M]$^+$) 332.1161, found 332.1161.

[2-(2-Methoxyquinolin-3-yl)-1*H*-indol-5-yl]-methanol. To a suspension of the methyl ester **19** (0.543 g, 1.63 mmol) in dry Et_2O (15 mL) at −15 °C was added $LiAlH_4$ (0.312 g, 8.2 mmol) in two portions under argon. The mixture was vigorously stirred under 0 °C for 5 h and then was quenched with NH_4Cl (10 mL). The mixture was extracted with EtOAc until no product was observed in the aqueous phase. The solution was washed with brine and dried over Na_2SO_4. The crude material was chromatographed with 50% EtOAc in hexanes to afford the product as a slightly yellow solid (0.471 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, s, br), 8.43 (1H, s), 8.43 (1H, s), 7.85 (1H, d, J = 8.3 Hz), 7.76 (1H, dd, J = 7.9, 1.3 Hz), 7.63−7.59 (2H, m), 7.44−7.39 (2H, m), 7.22 (1H, dd, J = 8.3, 1.5 Hz), 7.04 (1H, dd, J = 2.2, 0.9 Hz), 4.79 (2H, d, J = 5.7 Hz), 4.31 (3H, s), 1.58 (1H, t, J = 5.7 Hz); ^{13}C NMR (100 MHz, DMSO) δ 158.3, 145.4, 136.2, 135.4, 134.3, 133.1, 129.8, 128.4, 127.7, 127.2, 125.7, 125.0, 122.7, 119.5, 116.7, 111.6, 101.4, 66.5, 54.2; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_2$ ([M + H]$^+$) 305.1284, found 305.1281.

2-(2-Methoxyquinolin-3-yl)-1*H*-indole-5-carbaldehyde (20). To a mixture of the alcohol (0.266 g, 0.874 mmol), NMO (0.151 g, 1.31 mmol), and 4 Å molecular sieves (0.3 g) was added dry DCM (8.5 mL), and the resulting mixture was stirred at rt for 10 min before addition of TPAP (6.1 mg, 0.00175 mmol). The reaction mixture was stirred at rt for 24 h, quenched by addition of Na_2SO_3 (10 mL), and diluted with HOAc (20 mL). The organic phase was separated, washed with brine, and dried over Na_2SO_4. The crude material after removal of solvent was chromatographed with 25% EtOAc/hexnaes to afford a slightly yellow solid (0.241 g, 91%): mp 202−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (1H, s), 9.96 (1H, br), 8.52 (1H, s), 8.20 (1H, d, J = 0.7 Hz), 7.88 (1H, d, J = 8.3 Hz), 7.83−7.79 (2H, m), 7.66 (1H, ddd, J = 7.9, 7.0, 1.5 Hz), 7.55 (1H, d, J = 8.1 Hz), 7.45 (1H, ddd, J = 7.9, 7.9, 1.5 Hz), 7.22 (1H, dd, J = 2.2, 0.9 Hz), 4.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 158.1, 145.7, 139.9, 136.0, 135.8, 130.3, 130.2, 128.1, 127.8, 127.2, 125.9, 125.5, 125.2, 123.0, 115.9, 112.0, 102.7, 54.3; HRMS (ESI) calcd for $C_{19}H_{15}N_2O_2$ ([M + H]$^+$) 303.1128, found 303.1130.

3-[5-(4-Methanesulfonylpiperazin-1-ylmethyl)-1*H*-indol-2-yl]-2-methoxyquinoline (22). To a mixture of the aldehyde **20** (75.6 mg, 0.248 mmol), 1-methanesulfonylpiperazine (41 mg, 0.25 mmol), and 4 Å molecular sieves (0.1 g) was added DCM (5 mL), followed by $NaHB(OAc)_3$ (79.5 mg, 0.375 mmol). The resulting mixture was stirred at rt for 24 h. The mixture was filtered through a Celite pad and washed with EtOAc. The residue after removal of solvent was chromatographed with 100% EtOAc to afford a slightly yellow solid (0.1035 g, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, s), 8.43 (1H, s), 7.86 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 7.9 Hz), 7.61 (1H, t, J = 7.6 Hz), 7.54 (1H, s), 7.43−7.40 (2H, m), 7.17 (1H, d, J = 8.3 Hz), 7.03 (1H, s), 4.27 (3H, s), 3.64 (2H, s), 3.24 (4H, br), 2.75 (3H, s), 2.59 (4H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 145.5, 136.0, 135.4, 134.2, 129.8, 129.2, 128.3, 127.6, 127.2, 125.6, 125.0, 124.3, 121.2, 116.8, 111.3, 101.3, 63.4, 54.2, 52.4, 46.2, 34.2; HRMS (ESI) calcd for $C_{24}H_{27}N_4O_3S$ ([M + H]$^+$) 451.1798, found 451.1799.

3-[5-(4-Methanesulfonylpiperazin-1-ylmethyl)-1*H*-indol-2-yl]-1*H*-quinolin-2-one Hydrochloride (1). The literature procedure[7c] for the hydrolysis of the 2-methoxyquinoline was followed: A mixture of **22** (0.225 g, 0.5 mmol) and concd HCl (0.6 mL) in MeOH (4 mL) was heated under reflux (6 h) and stirred at rt overnight. The resulting suspension was filtered and washed with small portion of MeOH to afford the product as a yellow solid (0.225, 95%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (1H, s), 11.83 (1H, s), 11.05 (1H, s), 8.61 (1H, s), 7.79 (1H, s), 7.74 (1H, d, J = 7.5 Hz), 7.60 (1H, d, J = 8.3 Hz), 7.54 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 7.40 (2H, d, J = 9.0 Hz), 7.35 (1H, d, J = 7.5 Hz), 7.26 (1H, ddd, J = 7.5, 7.5, 1.1 Hz), 4.42 (2H, d, J = 4.2 Hz), 3.71 (2H, d, J = 12.7 Hz), 3.40 (2H, J = 12.0 Hz), 3.26 (2H, t, J = 11.9 Hz), 3.14 (2H, t, J = 11.8 Hz), 2.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 137.7, 137.0, 134.9, 130.5, 128.0, 128.0, 125.0, 123.8, 122.5, 122.2, 120.0, 119.4, 115.1, 112.1, 102.4, 59.7, 49.9, 42.4, 35.2; HRMS (EI) calcd for $C_{23}H_{25}N_4O_3S$ ([M + H]$^+$) 437.1641, found 437.1641.

5-(2-Methoxyethoxy)-2-nitrobenzaldehyde (26a). A 10-mL round-bottomed flask was charged with 5-hydroxy-2-nitrobenzaldhyde (0.668 g, 4 mmol) and K_2CO_3 (1.11 g, 8 mmol). After the mixture was purged with argon for 5 min, anhydrous DMF (3 mL) and 2-iodoethyl methyl ether (1.02 g, 6 mmol) were added, and the resulting mixture was heated at 75 °C overnight (12 h). The mixture was poured into 1 M NaOH (5 mL), extracted with Et_2O (3 × 20 mL), washed with $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), and dried over $MgSO_4$. The crude material was purified using silica gel column chromatography (33% EtOAc in hexanes) to afford the product **26a** as a slight yellow solid (0.881 g, 98%): mp 74−75 °C; IR (neat, cm^{-1}): 2898, 1693, 1586, 1511, 1334, 1282, 1248, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (1H, s), 8.16 (1H, d, J = 9.2 Hz), 7.36 (1H, d, J = 2.9 Hz), 7.20 (1H, dd, J = 9.1, 3.0 Hz), 4.28−4.26 (2H, m), 3.81−3.78 (2H, m), 3.46 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 163.4, 142.4, 134.4, 127.4, 119.3, 113.9, 70.6, 68.7, 59.4; HRMS (EI) calcd for $C_{10}H_{12}NO_5$ ([M + H]$^+$) 226.0715, found 226.0715.

2-(2,2-Dibromovinyl)-4-(2-methoxyethoxy)-1-nitrobenzene (28a). To a solution of the aldehyde **26a** (0.122 g, 0.5 mmol) and CBr_4 (0.250 g, 0.75 mmol) in DCM (3 mL) was added a solution of PPh_3 (0.393 g, 1.5 mmol) in DCM (1 mL) at 0 °C. The mixture was stirred for 30 min, warmed to rt, and quenched with $NaHCO_3$ (5 mL). The resulting mixture was extracted with Et_2O (15 mL) and EtOAc (15 mL). The organic layer was washed with brine and dried over $MgSO_4$. The crude material was purified by flash chromatography to afford **28a** as a slightly yellow solid (0.1553 g, 80%): mp 97−98 °C; IR (neat, cm^{-1}) 2911, 1582, 1509, 1332, 1243, 1126, 1078; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, d, J = 9.0 Hz), 7.79 (1H, d, J = 0.6 Hz), 7.04 (1H, dd, J = 1.8, 0.6 Hz), 7.01 (1H, dd, J = 9.2, 1.8 Hz), 4.24−4.22 (2H, m), 3.80−3.78 (2H, m), 3.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 140.1, 134.9, 134.1, 127.7, 117.0, 115.3, 92.8, 70.8, 68.5, 59.5; HRMS (EI) calcd for $C_{11}H_{11}NO_4Br_2$ ([M]$^+$) 378.9055, found 378.9076.

2-(2,2-Dibromovinyl)-4-(2-methoxyethoxy)phenylamine (29a). A mixture of the nitrobenzene (0.155 g, 0.41 mmol) and 1% Pt−C [V] (15 mg) in MeOH (5 mL) was hydrogenated at 50 psi for 15 h using a Parr hydrogenator. After removal of the catalyst through filtration, solvent was evaporated, and the residue was purified by flash chromatography with 20% → 25% EtOAc in hexanes to afford **29a** as a colorless oil (0.118 g, 79%): IR (neat, cm^{-1}) 3439, 3357, 2924, 2880, 1609, 1497, 1259, 1228, 1124. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, t, J = 0.6 Hz), 6.94 (1H, d, J = 2.9 Hz), 6.81 (1H, ddd, J = 8.7, 2.9, 0.5 Hz), 6.65 (1H, d, J = 8.7 Hz), 4.07−4.05 (2H, m), 3.73−3.71 (2H, m), 3.46 (2H, br), 3.45 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 137.8, 134.0, 122.7, 117.4, 114.9, 92.7, 71.3, 68.2, 59.3; HRMS calcd for $C_{11}H_{14}NO_2Br_2$ ([M + H]$^+$) 349.9385, found 349.9375.

2-Methoxy-3-[5-(2-methoxyethoxy)-1*H*-indol-2-yl]quinoline (30a). A 10 mL round-bottomed flask was charged with substrate **29a** (0.118 g, 0.323 mmol), boronic acid **13** (0.098 g, 0.48 mmol), and $K_3PO_4 \cdot H_2O$. After the flask was purged with argon for 10 min, a solution of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and S-Phos (8.2 mg, 0.02 mmol) in PhMe (1.5 mL) was cannulated into the reaction mixture. After heating to 100 °C for 1.5 h, the reaction was quenched by addition of $NaHCO_3$, extracted with EtOAc (3 × 10 mL), and dried over Na_2SO_4. The crude material was purified by flash chromatography using 25% EtOAc in hexanes to afford **30a** as a slightly yellow oil (0.0831 g, 74%): IR (neat, cm^{-1}) 3454, 3389, 2924, 1622, 1476, 1451, 1398, 1213, 1194, 1120; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, br), 8.38 (1H, s), 7.84 (1H, d, J = 8.3 Hz), 7.73 (1H, dd, J = 8.0, 1.2 Hz), 7.59 (1H, ddd, J = 8.2, 7.0, 1.5 Hz), 7.39 (1H, ddd, J = 7.9, 7.0, 1.1 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.11 (1H, d, J = 2.4 Hz), 6.97 (1H, dd, J = 2.2, 0.9 Hz), 6.93 (1H, dd, J = 8.8, 2.4 Hz), 4.24 (3H, s), 4.19−4.17 (2H, m), 3.80−3.77 (2H, m), 3.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 153.8, 145.3, 135.1, 134.3, 132.1, 129.6, 128.7, 127.6, 127.1, 125.7, 124.9, 116.9, 114.0, 112.1, 103.2, 101.2, 71.5, 68.2, 59.4, 54.2; HRMS calcd for $C_{21}H_{21}N_2O_3$ ($[M + H]^+$) 349.1546, found 349.1540.

3-[5-(2-Methoxyethoxy)-1*H*-indol-2-yl]-1*H*-quinolin-2-one (4). A mixture of **30a** (45 mg, 0.129 mmol) and HCl (3 mL, 3 M) was heated at 90 °C overnight. Solid K_2CO_3 was carefully added to the mixture until the pH > 7, and the resulting mixture was filtered. The solid collected was purified by flash chromatography using 50% EtOAc in hexanes (column length 5 cm) to afford the product as a yellow solid (41 mg, 95%): ^1H NMR (400 MHz, DMSO-d_6) δ 12.15 (1H, s), 11.43 (1H, s), 8.51 (1H, s), 7.73 (1H, d, J = 7.9 Hz), 7.51 (1H, d, J = 7.8 Hz), 7.42 (1H, d, J = 9.0 Hz), 7.37 (1H, d, J = 8.1 Hz), 7.24 (1H, t, J = 7.5 Hz), 7.22 (1H, s), 7.05 (1H, d, J = 2.2 Hz), 6.77 (1H, dd, J = 8.5, 2.1 Hz), 4.09 (2H, t, J = 4.5 Hz), 3.68 (2H, t, J = 4.5 Hz), 3.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 152.7, 137.5, 134.1, 133.7, 131.9, 130.0, 128.2, 127.7, 122.5, 122.3, 119.5, 114.9, 112.9, 112.5, 102.3, 101.7, 101.7, 70.7, 67.2, 58.2; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_3$ ($[M + H]^+$) 335.1390, found 335.1390.

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Supporting Information Available: Experimental procedure and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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