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# Synthesis of an indole containing KDR kinase inhibitor by tandem Sonogashira coupling-5-*endo-dig*-cyclization as a key step

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**Abstract**—An efficient synthesis of the potent KDR kinase inhibitor 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline-2-(1*H*)-one using a Sonogashira coupling-5-*endo-dig*-cyclization strategy is described.


## 1. Introduction

The substituted indole nucleus is a structural component of a vast number of biologically active natural and unnatural compounds. Due to the existence of an array of structurally diverse and biologically active indoles, it is not surprising that the indole nucleus is an important feature in many therapeutic agents.[1]

Recently Merck reported a class of potent KDR kinase inhibitors containing indol-2-yl quinoline-2-one as the key pharmacophore.[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.[4] Compound **1** was found to be of use in the treatment of certain types of cancer.[3]

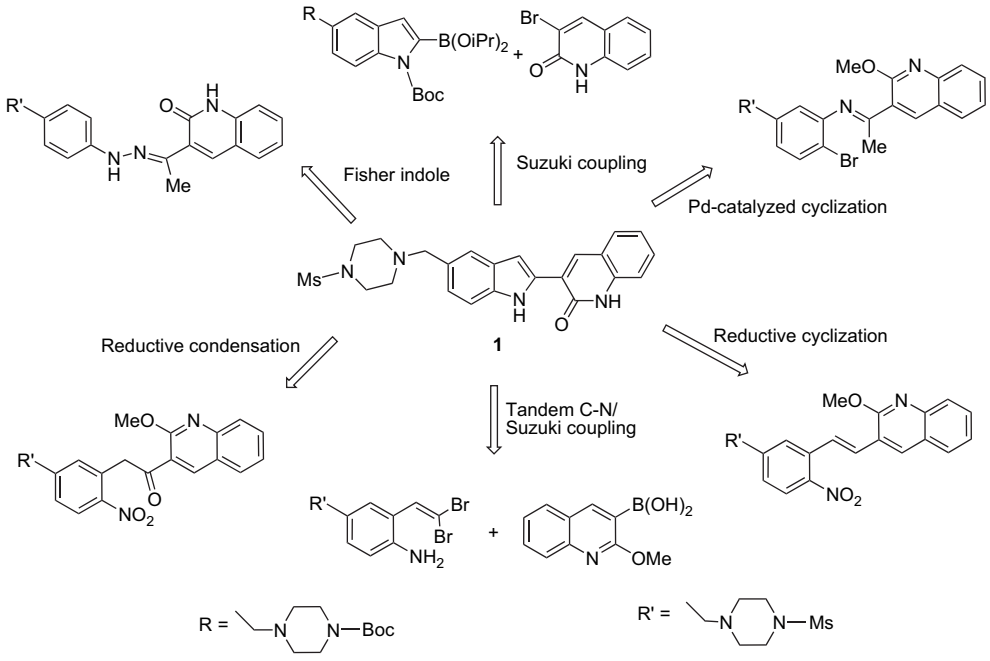


**Figure 1**. Reported retrosynthetic key steps for KDR **1**.

*Keywords*: Indol-2-yl quinoline-2-one; Synthesis; 5-*endo-dig*-Cyclization; KDR kinase inhibitor.
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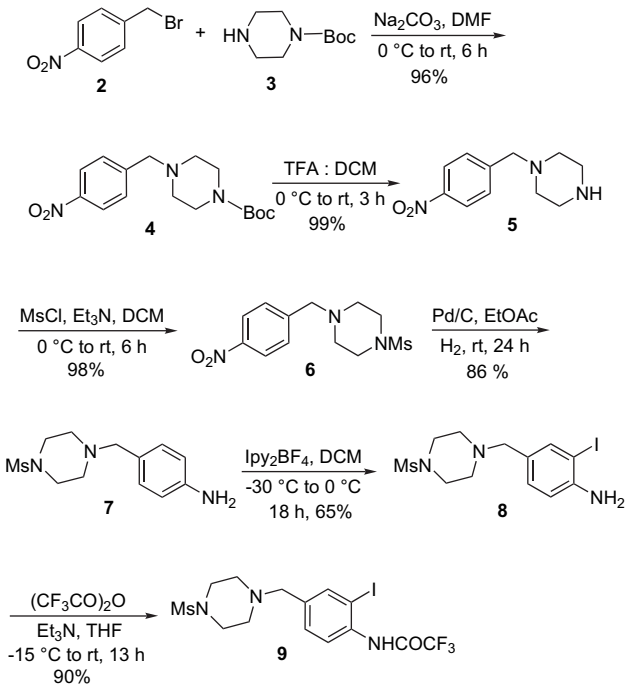
Various methods for the synthesis of compound **1** have been reported (Fig. 1) in the literature such as Suzuki coupling, reductive condensation of nitroketone, Fischer indole synthesis, palladium-catalyzed cyclization of imine, and cyclization of nitrostyrene.[2a] Very recently the synthesis of compound **1** using palladium-catalyzed tandem C–N/Suzuki coupling reaction has been reported by Lautens et al.[4] Palladium-catalyzed annulation of *o*-halo anilines with terminal alkynes under Sonogashira reaction conditions has been employed widely due to the versatile nature of these protocols, increased functional group tolerance, and improved yields. Recently, we have reported a novel synthesis of indoles under mild conditions employing a Sonogashira coupling-5-*endo-dig*-cyclization protocol.[5] In continuation of these studies, we wish to report the adaptation of this general methodology to the synthesis of KDR kinase inhibitor **1**.

## 2. Results and discussion

A retrosynthetic analysis of **1** revealed that the synthesis of **1** could be achieved by a Sonogashira coupling-5-*endo-dig*-cyclization (Scheme 1). A tandem coupling–cyclization between substituted *o*-anilide **9** and 2-chloro-3-ethynyl quinoline **13** would give the indole-chloroquinoline **14**. The indole-chloroquinoline **14**, which is known to readily hydrolyze upon treatment with a 1:1 mixture of acetic acid/water, will give the indole-quinolone core.[2a]

The *o*-iodoanilide fragment **9** was conveniently constructed from the commercially available 4-nitrobenzyl bromide **2** and *N*-Boc piperazine **3** in six reaction steps (Scheme 2).

The reaction of **2** with **3** for 6 h in DMF in the presence of $Na_2CO_3$ at room temperature afforded the nitro derivative **4** in 96% yield (isolated). Deprotection of *N*-Boc group in DCM by using TFA and subsequent mesylation of –NH group afforded the mesyl derivative **6** in 98% yield. The catalytic hydrogenation of **6** by using 10 mol % Pd/C in ethyl acetate gave the aniline **7** in 86% yield (isolated). The aniline **7** is iodinated regioselectively at the *ortho* position by using $Ipy_2BF_4$.[6] When iodination was carried out at room temperature with dropwise addition of iodinating reagent in DCM, the procedure gives only 35% desired *o*-iodoaniline **8** along with 20% diiodo derivative. In order to avoid diiodination and achieve better regioselectivity and yield in the formation of **8**, the conditions for the iodination were optimized. After a number of experiments were carried out at different temperatures under the slow addition of an iodinating reagent

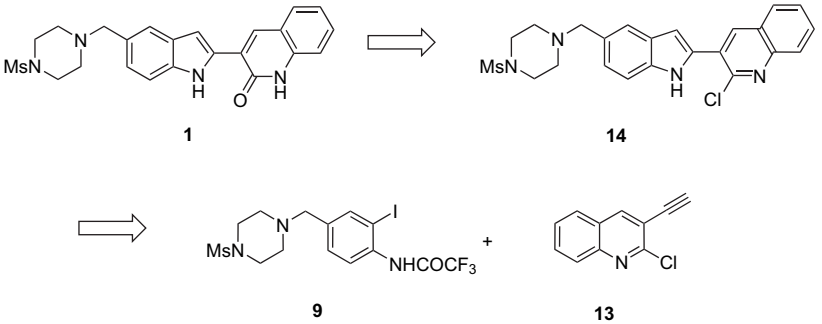



**Scheme 2**.

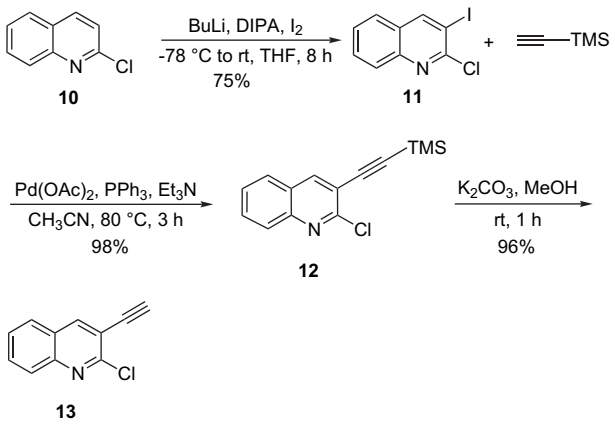
solution in DCM, it was found that the best condition for the iodination was the reaction carried out at −30 °C with dropwise addition of the iodinating reagent solution in DCM to afford regioselectively the *o*-iodoaniline derivative **8** in 65% yield (isolated). In order to achieve coupling–cyclization and deprotection smoothly in one-pot, *o*-iodoaniline **8** was protected by trifluoroacetyl group. The trifluoroacetyl derivative **9** of the *o*-iodoaniline **8** was prepared in excellent yield (90%) according to the procedure given in the literature.[7] The overall yield of **9** is 47% over six linear steps.

The synthesis of the other coupling partner 2-chloro-3-ethynyl quinoline **13** was successfully accomplished starting from the commercially available 2-chloroquinoline (Scheme 3).

The regioselective iodination of 2-chloroquinoline at the 3-position was carried out using a literature procedure[8] to give 2-chloro-3-iodoquinoline **11** as colorless solid in good yield (75%). Furthermore the regioselective coupling of **11** with trimethylsilyl acetylene was performed in the presence of catalytic amount of $Pd(OAc)_2$, using $PPh_3$ as ligand in acetonitrile employing $Et_3N$ as the base to afford TMS protected



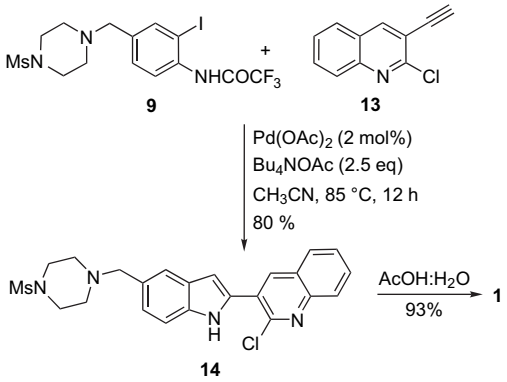

**Scheme 1**. Retrosynthetic key steps for the synthesis of KDR kinase inhibitor **1**.




**Scheme 3**.

alkyne **12** as colorless solid in excellent yield (98%). The deprotection of TMS group by using catalytic amount of $K_2CO_3$ in methanol afforded the terminal alkyne fragment **13** as colorless crystalline solid in excellent isolated yield (96%).

Palladium-catalyzed tandem Sonogashira coupling-5-*endo-dig*-cyclization of *o*-iodoanilide derivative **9** with terminal alkyne **13** proceeded smoothly in acetonitrile by using $Pd(OAc)_2$ as the pre-catalyst, $Bu_4NOAc$ as the base under ligand-, copper-, and amine-free conditions[5] to give the indole-chloroquinoline **14** as a pale yellow foamy solid in good yield (80%) (Scheme 4).




**Scheme 4**. Sonogashira coupling-5-*endo-dig*-cyclization.

The deprotection of the masked quinolin-2-one moiety of chloroquinoline **14** to get target compound **1** was accomplished in a straightforward manner under acidic conditions. Hydrolysis of chloroquinoline **14** in a 1:1 mixture of acetic acid/water as per the method reported in the literature[2a] gave KDR inhibitor **1** in 93% yield. All the compounds were well characterized by $^1H$ and $^{13}C$ NMR spectroscopies, elemental analysis, IR, and LC–MS. The structure of **1** was confirmed by comparing its characterization data with literature data,[2b] which was found to be identical.

## 3. Conclusion

In conclusion, we have developed a new alternative route to the synthesis of the potent and selective KDR kinase inhibitor **1** using Sonogashira coupling-5-*endo-dig*-cyclization strategy. The overall yield of compound **1** was 35% with respect to **2** in eight linear steps.

## 4. Experimental section

### 4.1. General

All reactions requiring anhydrous conditions were performed under positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. DCM, acetonitrile, and triethyl amine were distilled from $CaH_2$ and stored over molecular sieves and KOH, respectively. Melting points were recorded in open capillary using Buchi melting point B-540 apparatus. Column chromatography was performed using silica gel (60–120 mesh size and 230–400 mesh size for flash column chromatography) and TLC was carried out using aluminum sheets precoated with silica gel $60F_{254}$ (Merck). All chemicals used were reagent grade procured commercially and used without further purification. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance DPX 200 spectrometer by using TMS as internal standard. Infrared spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer. Elemental analysis was performed on Flash EA 1112 Thermo Finnigan instrument.

**4.1.1. *t*ert-Butyl-4-(4-nitrobenzyl)piperazine-1-carboxylate (4).**[2a] White solid; mp 98–99 °C; IR (neat, $cm^{-1}$) 3019, 2400, 1685, 1523, 1346, 1216, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.46 (s, 9H), 2.39–2.44 (m, 4H), 3.43–3.48 (m, 4H), 3.61 (s, 2H), 7.53 (d, 2H, $J$=8.60 Hz), 8.19 (d, 2H, $J$=8.74 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 28.4, 52.9, 62.1, 76.7, 123.5, 129.4, 145.9, 147.2, 154.7. Anal. Calcd for $C_{16}H_{23}N_3O_4$: C, 59.80; H, 7.21; N, 13.08. Found: C, 59.46; H, 7.31; N, 13.17. LC–MS calcd for $C_{16}H_{23}N_3O_4$ ($[M+H]^+$) 322.17, found 322.1352.

**4.1.2. 1-Methanesulfonyl-4-(4-nitrobenzyl)-piperazine (6).** To a solution of **4** (8.28 g, 25.7 mmol) in DCM (10 mL) at 0 °C was added dropwise TFA (10 mL). After stirring for 3 h at room temperature, the reaction mixture was neutralized with 10% aqueous NaOH to a pH of 8.0 and extracted with DCM. The extract was dried over $MgSO_4$ and concentrated under reduced pressure, to afford 5.62 g of crude **5** (99%) as a colorless solid, which was used directly in the next step without further purification as follows: To a mixture of above deprotected product **5** (5.62 g, 25.5 mmol) and $Et_3N$ (2.83 g, 28.0 mmol) in dry DCM (20 mL) at 0 °C was added dropwise methanesulfonyl chloride (3.96 g, 28.0 mmol). The resulting reaction mixture was further stirred for 6 h at room temperature, neutralized with 10% aqueous NaOH, and then extracted with DCM. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, by eluting with 70% ethyl acetate/petroleum ether to afford 7.48 g 0f **6** (98%) as a colorless solid. Mp 133–135 °C (lit. 116–117 °C);[2a] IR (neat, $cm^{-1}$) 3023, 1606, 1521, 1347, 962, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.56–2.61 (m, 4H), 2.81 (s, 3H), 3.25–3.30 (m, 4H), 3.66 (s, 2H), 7.53 (d, 2H, $J$=8.84 Hz), 8.19 (d, 2H, $J$=8.88 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 34.2, 45.7, 52.2, 61.5, 123.5,

129.4, 145.4, 147.2. Anal. Calcd for $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.72; N, 14.04. Found: C, 48.36; H, 5.70; N, 13.66. LC–MS calcd for $C_{12}H_{17}N_3O_4S$ ($[M+H]^+$) 300.09, found 300.9906.

**4.1.3. 4-(4-Methanesulfonyl piperazine-1-yl-methyl)-aniline (7).**[2a] Colorless solid; mp 168–169 °C (lit. 161–162 °C);[2a] IR (neat, $cm^{-1}$) 3393, 3020, 2400, 1622, 1518, 1324, 1215, 961, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.50–2.55 (m, 4H), 2.76 (s, 3H), 3.20–3.25 (m, 4H), 3.43 (s, 2H), 6.64 (d, 2H, $J$=8.37 Hz), 7.07 (d, 2H, $J$=8.37 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 34.0, 45.8, 51.9, 62.1, 114.8, 126.9, 130.2, 145.7. Anal. Calcd for $C_{12}H_{19}N_3O_2S$: C, 53.51; H, 7.11; N, 15.60. Found: C, 53.71; H, 6.81; N, 15.23.

**4.1.4. 2-Iodo-4-(4-methanesulfonylpiperazine-1-yl-methyl)aniline (8).** To a solution of **7** (2.0 g, 7.43 mmol) in DCM (50 mL) at −30 °C was added dropwise $Ipy_2BF_4$ (2.76 g, 7.43 mmol) solution in DCM (20 mL) over a period of 6 h. The reaction mixture was further stirred for 1 h at the same temperature. After stirring for 1 h at −30 °C, the reaction mixture was allowed to warm up to 0 °C and stirred overnight. After the completion of reaction, solvent was removed under reduced pressure. The residue was purified by silica gel chromatography, by eluting with 75% ethyl acetate/petroleum ether to afford 1.90 g of **8** (65%) as a colorless solid. Mp 185–187 °C; IR (neat, $cm^{-1}$) 3480, 3387, 3133, 3019, 2400, 1617, 1500, 1318, 1215, 1071, 757, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.52–2.57 (m, 4H), 2.78 (s, 3H), 3.22–3.27 (m, 4H), 3.41 (s, 2H), 6.70 (d, 1H, $J$=8.06 Hz), 7.06 (dd, 1H, $J$=6.17, 1.94 Hz), 7.58 (d, 1H, $J$=1.72 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 34.1, 45.7, 51.9, 61.2, 83.9, 114.3, 128.6, 130.4, 139.4 146.1. Anal. Calcd for $C_{12}H_{18}IN_3O_2S$: C, 36.54; H, 4.56; N, 10.65. Found: C, 36.40; H, 4.52; N, 10.62. LC–MS calcd for $C_{12}H_{18}IN_3O_2S$ $[M]^+$ 395.02, found 395.92.

**4.1.5. 2-Iodo-4-(4-methanesulfonyl piperazine-1-yl-methyl)trifluoroacetanilide (9).** The literature procedure[7] for the preparation of trifluoroacetyl derivative **9** of *o*-iodoaniline derivative **8** was followed: To a stirred solution of **8** (0.8 g, 2.03 mmol) and $Et_3N$ (0.3 mL, 2.15 mmol) in THF (5 mL) at −15 °C was added dropwise $(CF_3CO)_2O$ (0.426 g, 2.03 mmol) solution in THF (3 mL). After 1 h of stirring at −15 °C, the reaction mixture was allowed to warm up to room temperature, stirred overnight, and then poured into a separatory funnel containing water (50 mL). The product was extracted into ethyl acetate, the combined organic layer was then dried over $MgSO_4$, the solvent was evaporated, and product chromatographed with 60% ethyl acetate in petroleum ether to afford 0.89 g of **9** (90%) as a colorless solid. Mp 124–126 °C; IR (neat, $cm^{-1}$) 3363, 3022, 2401, 1736, 1536, 1348, 1215, 962, 756, 667; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.50–2.54 (m, 4H), 2.73 (s, 3H), 3.19–3.23 (m, 4H), 3.46 (s, 2H), 7.30 (dd, 1H, $J$=8.30, 1.66 Hz), 7.76 (d, 1H, $J$=1.82 Hz), 7.09 (d, 1H, $J$=8.45 Hz), 8.20 (br s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 34.3, 45.6, 52.2, 60.9, 90.4, 114.4, 116.7, 121.8, 130.2, 134.9, 139.4, 154.9. Anal. Calcd for $C_{14}H_{17}F_3IN_3O_3S$: C, 34.23; H, 3.49; N, 8.55. Found: C, 34.26; H, 3.61; N, 8.72. LC–MS calcd for $C_{14}H_{17}F_3IN_3O_3S$ ($[M+H]^+$) 492, found 491.99.

**4.1.6. 2-Chloro-3-iodoquinoline (11).**[8] *n*-BuLi (1.6 M in hexane, 19 mL, 50 mmol) was slowly added to a magnetically stirred solution of diisopropylamine (3.07 g, 50 mmol) in dry THF (100 mL) under argon at −78 °C. The solution of LDA was stirred at −78 °C for 1 h. 2-Chloroquinoline (5 g, 30 mmol) in THF (25 mL) was added slowly to the reaction mixture at −78 °C and stirred for 4 h at the same temperature at −78 °C. The iodine solution (9.25 g, 36.7 mmol) in THF (40 mL) was slowly added to a solution of lithiated 2-chloroquinoline. The resulting solution was stirred for 2 h at −78 °C and allowed to warm to room temperature over 5 h. After removing the solvent under reduced pressure, the residue was extracted using $Et_2O$ and decolorized with saturated $NaHSO_3$ aqueous solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography, by eluting with 1% ethyl acetate/petroleum ether, to afford 6.49 g of **11** (75%) as a colorless solid. Mp 144–145 °C (lit. 145–146 °C);[8] IR (neat, $cm^{-1}$) 3018, 2400, 1548, 1487, 1361, 1215, 952, 755, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 7.49–7.57 (m, 1H), 7.65–7.75 (m, 2H), 7.95 (d, 1H, $J$=8.95 Hz), 8.60 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 90.9, 126.3, 127.6, 128.4, 130.9, 146.7, 148.5, 152.2. Anal. Calcd for $C_9H_5ClIN$: C, 37.34; H, 1.74; N, 4.84. Found: C, 37.68; H, 1.90; N, 4.95.

**4.1.7. 2-Chloro-3-[2-(trimethylsilyl)ethynyl]quinoline (12).** A mixture of **11** (0.5 g, 1.76 mmol), trimethylsilylacetylene (0.258 g, 2.64 mmol), $Pd(OAc)_2$ (3.9 mg, 1 mol %), $PPh_3$ (9.1 mg, 2 mol %), and $Et_3N$ (0.889 g, 8.80 mmol) in acetonitrile (5 mL) was heated at 80 °C for 3 h under argon atmosphere. After the completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography by eluting with 1% ethyl acetate in petroleum ether to afford 0.448 g of **13** (98%) as a colorless solid. Mp 96–97 °C; IR (neat, $cm^{-1}$) 3018, 2400, 2160, 1618, 1487, 1336, 1215, 858, 760, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.31 (s, 9H), 7.49–7.57 (m, 1H), 7.66–7.76 (m, 2H), 7.97 (d, 1H, $J$=8.31 Hz), 8.27 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ −0.32, 99.7, 102.4, 117.7, 126.2, 127.2, 127.4, 128.5, 131.1, 141.7, 146.3, 150.6. Anal. Calcd for $C_{14}H_{14}ClNSi$: C, 64.72; H, 5.43; N, 5.39. Found: C, 65.10; H, 5.40; N, 5.71. LC–MS calcd for $C_{14}H_{14}ClNSi$ ($[M+H]^+$) 259.06, found 260.035.

**4.1.8. 2-Chloro-3-ethynyl quinoline (13).** To a solution of **12** (0.4 g, 1.53 mmol) in methanol (5 mL) was added $K_2CO_3$ (5 mg, 2 mol %). The resulting reaction mixture was stirred at room temperature under an atmosphere of argon for 1 h. Then the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography by eluting with 3% ethyl acetate in petroleum ether to afford 0.277 g of **13** (96%) as a colorless solid. Mp 115–116 °C; IR (neat, $cm^{-1}$) 3304, 3018, 2400, 1619, 1487, 1339, 1215, 1040, 756, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 3.50 (s, 9H), 7.54–7.62 (m, 1H), 7.71–7.80 (m, 2H), 7.98–8.03 (m, 1H), 8.33 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 78.7, 83.9, 116.5, 125.8, 127.0, 127.4, 128.2, 131.2, 142.3, 146.3, 150.2. Anal. Calcd for $C_{11}H_6ClN$: C, 70.42; H, 3.22; N, 7.47. Found: C, 70.32; H, 3.22; N, 7.47. LC–MS calcd for $C_{11}H_6ClN$ $[M+H]^+$ 188.02, found 187.97.

**4.1.9. 2-Chloro-3-[5-[[4-(methysulfonyl)-1-piperazinyl]-methyl]-1*H*-indol-2-yl]-quinoline (14).** A mixture of **9** (0.2 g, 0.40 mmol), **13** (0.085 g, 0.49 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %), and $Bu_4NOAc$ (0.307 g, 1.01 mmol) in acetonitrile (5 mL) was heated at 85 °C to reflux under an atmosphere of argon for 12 h. After the completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography by using 60% ethyl acetate in petroleum ether as the eluent system to afford 0.149 g of **14** (80%) as a pale yellow foamy solid. Mp 108–110 °C; IR (neat, $cm^{-1}$) 3467, 3019, 2400, 1670, 1346, 1328, 1215, 1159, 960, 756, 668; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.61–2.66 (m, 4H), 2.78 (s, 3H), 3.26–3.30 (m, 4H), 3.70 (s, 2H), 6.96 (s, 1H), 7.25 (d, 1H, $J$=9.79 Hz), 7.44 (d, 1H, $J$=8.24 Hz), 7.56–7.64 (m, 2H), 7.76 (t, 1H, $J$=8.58 Hz), 7.87 (d, 1H, $J$=9.12 Hz), 8.05 (d, 1H, $J$=7.88 Hz), 8.41 (s, 1H), 8.92 (br s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 34.1, 45.8, 52.1, 62.9, 104.7, 111.2, 121.5, 124.7, 125.8, 127.0, 127.5, 127.6, 128.1, 128.3, 130.8, 134.4, 136.3, 138.3, 146.6, 147.6. Anal. Calcd for $C_{23}H_{23}ClN_4O_2S$: C, 60.72; H, 5.10; Cl, 7.79; N, 12.31; S, 7.05. Found: C, 60.32; H, 5.17; N, 11.93; S, 6.65. LC–MS calcd for $C_{23}H_{23}ClN_4O_2S$ ($[M+H]^+$) 455.12, found 455.1413.

**4.1.10. 3-[5-[[4-(Methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline-2-(1*H*)-one (1).** Compound **14** (50 mg, 0.11 mmol) in a mixture of AcOH (1 mL) and $H_2O$ (1 mL) was heated at 100 °C for 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash column chromatography by eluting with ethyl acetate to afford 44 mg of **1** (93%) as a yellow solid. Mp 273–275 °C (lit. 275–277 °C);[2b] IR (neat, $cm^{-1}$) 3454, 2924, 2854, 1651, 1462, 1376, 1167, 961; $^1H$ NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.43 (s, 4H), 2.79 (s, 3H), 3.02 (s, 4H), 3.51 (s, 2H), 7.25 (t, 1H, $J$=7.57, 7.01 Hz), 7.36 (d, 2H, $J$=4.28 Hz), 7.39 (d, 1H, $J$=8.26 Hz), 7.51 (s, 1H), 7.54 (d, 1H, $J$=8.53 Hz), 7.73 (d, 1H, $J$=7.74 Hz), 7.79 (s, 1H), 8.55 (s, 1H), 11.71 (s, 1H), 12.28 (br s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 50 MHz) $\delta$ 35.0, 45.8, 55.3, 61.7, 102.7, 111.7, 115.4, 119.8, 120.7, 122.7, 122.8, 125.5, 127.1, 128.0, 128.3, 128.6, 130.7, 132.8, 134.8, 134.9, 137.3, 138.1, 161.0. Anal. Calcd for $C_{23}H_{24}N_4O_3S$: C, 63.28; H, 5.54; N, 12.83; S, 7.33. Found: C, 63.07; H, 5.50; N, 12.72.

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## References and notes

1. (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, NY, 1970; (b) Sundberg, R. J. Pyrroles and their Benzoderivatives: Synthesis and Applications. *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: New York, NY, 1996; pp 7–11; (d) Joule, J. A. Indole and its Derivatives. *Science of Synthesis: Houben–Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; George Thieme: Stuttgart, Germany, 2000; Vol. 10, Category 2, Chapter 10.13; (e) Brown, R. K. *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, NY, 1972.
2. (a) Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555; (b) Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175; (c) Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 7761; (d) Davies, I. W.; Smitrovich, J. H.; Qu, C. PCT Int. Appl. WO 2005000804, Merck: USA, 2005; (e) Karki, S. B.; Deshpande, S. R.; Thompson, K. C.; Payne, A. H.; Gandek, T. P. PCT Int. Appl. WO 2004087651, Merck: USA, 2004; (f) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975; (g) Fraley, M. E.; 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.
3. (a) Fraley, M. E.; Arrington, K. L.; Bilodeau, M. T.; Hartman, G. A.; Hoffman, W. F.; Kin, Y.; Hungate, R. W., US Patent 6,306,874 B1, 2001; (b) Fraley, M. E. Presented at the 29th National Medicinal Chemistry Symposium, Madison, WI, June 2004; Abstract 14.
4. Fang, Y.-Q.; Karisch, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341.
5. Palimkar, S. S.; Harish Kumar, P.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2006**, *62*, 5109.
6. Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804.
7. Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017.
8. Gee, M. B.; Lee, W. J.; Yum, E. K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1193.