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A Concise Synthesis of a Novel Antiangiogenic Tyrosine Kinase Inhibitor

Joseph F. Payack,* Enrique Vazquez,* Louis Matty, Michael H. Kress, and James McNamara

Department of Process Research, Merck & Co. Inc., P.O. Box 2000, Rahway, New Jersey 07065-0900

joseph_payack@merck.com

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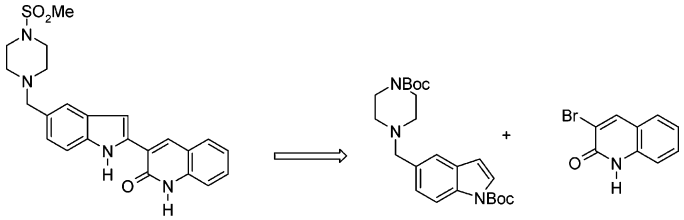

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An efficient synthesis of the potent KDR inhibitor 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indole-2-yl]quinolin-2(1*H*)-one (**1**) is described. The process features a noncryogenic indole boronation and a dicyclohexylamine-mediated Suzuki coupling.

Introduction

Anti-angiogenic chemotherapy has emerged as a promising area in clinical oncology.[1] By preventing the neovascularization of hypoxic regions within a tumor, neoplastic growth may be slowed or even reversed.[2] Vascular endothelial growth factor (VEGF) is believed to be one of the primary mediators of tumor-induced angiogenesis, and inhibition of VEGF is an active area in angiogenesis research.[3] KDR, a tyrosine kinase, is the VEGF receptor expressed on activated endothelial cells and is thus an attractive target for inhibition.[4] We present here an efficient convergent synthesis of the potent and selective KDR inhibitor 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]-methyl]-1*H*-indole-2-yl]quinolin-2(1*H*)-one (**1**)[5] based on a Suzuki coupling of two advanced intermediates. While another synthesis of **1** has been described,[6] this concise and convergent route produced bulk supplies for development.

Results and Discussion

Retrosynthetic analysis revealed that the most efficient route to **1** would employ a late-stage cross coupling of the indole and quinolinone fragments (Scheme 1). This convergent approach allowed for maximum flexibility during development. The indole fragment **2** was conveniently constructed from commercially available 5-cyanoindole via a three-step, one-pot sequence in toluene, in 80% overall yield (Scheme 2). After initial protection with Boc-anhydride, the nitrile was reduced to the imine via a slow addition of DIBAL-H at ~20 °C. A 3 h addition ensures that nitrile over-reduction to the primary amine was minimized. An extra equivalent of DIBAL-H was necessary due to the presence of 1 equiv of *tert*-butyl alcohol produced in the Boc protection step. The reduction was quenched into a concentrated aqueous solution of sodium hydrogen sulfate, which was acidic enough to dissolve the aluminum salts, but was compatible with the acid-sensitive Boc moiety. The acidic system efficiently hydrolyzed the imine to the aldehyde. After drying, the Boc-piperazine fragment was smoothly introduced via a sodium triacetoxyborohydride mediated reductive amination. After an aqueous workup, intermediate **2** was isolated via crystallization from methanol.

Fragment **3** was prepared via a modified literature procedure[7] from 3-bromoquinoline (Scheme 3). The sequence proceeds via the formation of the quinoline *N*-oxide, followed by acid chloride mediated 1,2 oxygen

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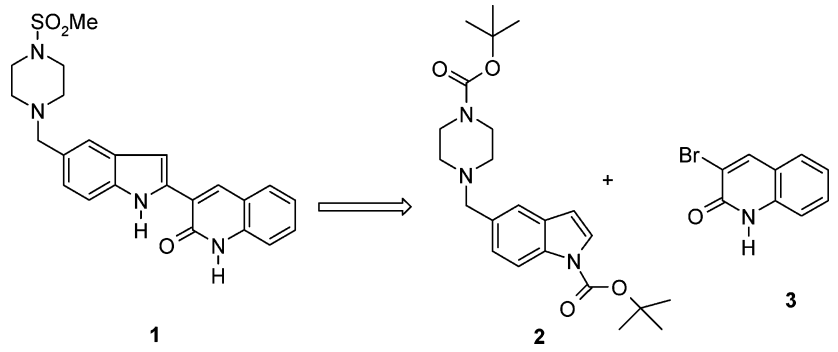
SCHEME 1



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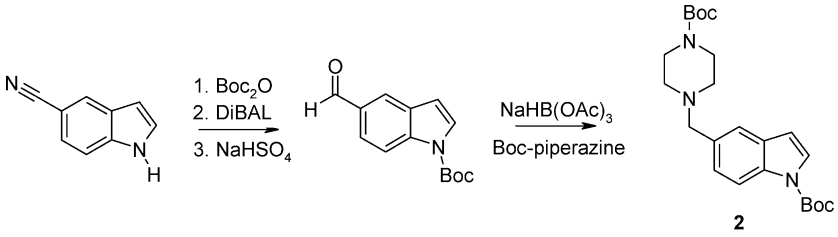

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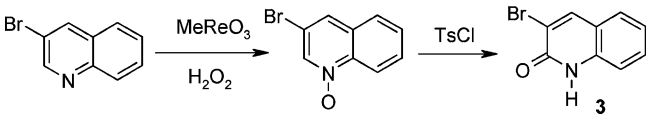

rearrangement. Initially, we produced the *N*-oxide via *m*-CPBA; however, safety concerns led us to consider alternate oxidation conditions. The methyltrioxorhenium/hydrogen peroxide protocol developed by Murray and Sharpless[8] proved to be an excellent alternative. The *N*-oxide was made using 0.5 mol % catalyst and 3 equiv of H_2O_2 in THF at ambient temperature. Careful addition of 20 wt % aqueous sodium sulfite quenched the remaining peroxide, and after an aqueous workup, the intermediate was dissolved in ethyl acetate. Treatment with *p*-toluenesulfonyl chloride and aqueous potassium carbonate smoothly effected the rearrangement, and the product **3** crystallized as the ambient temperature reaction proceeded. Filtration afforded highly pure **3** in 80% overall yield.

The key step of the sequence was a Suzuki−Miyaura[9] coupling between the 2-boronic acid derivative of indole **2** with bromide **3** (Scheme 4). The indole was lithiated selectively at the 2-position and was quenched in situ by triisopropyl borate using the noncryogenic protocol developed in our laboratory.[10] The cross-coupling was run in THF with palladium acetate (0.5 mol %) and triphenylphosphine; however, the usual basic aqueous system led to substantial deboronation. Dicyclohexylamine was found to be an excellent activator, and after refinement, excellent yields of the coupled product **4** were obtained. A key observation was that slow addition of a solution of the boronic acid to the catalyst/bromoquinolinone mixture minimized deboronation. The coupled material was isolated via carbon treatment, filtration, and direct crystallization from the reaction mixture using hexanes as an antisolvent to afford the product **4** in 88% yield as a mixture with salts. An aqueous carbon treatment followed by crystallization was optimized to remove the palladium and salts to give analytically pure material.

Deprotection of **4** was smoothly accomplished by treatment with aq HCl in 65 °C ethanol to provide **5** as its crystalline bis-HCl salt. To complete the synthesis, a mesyl group must be appended to the piperazine. This seemingly trivial transformation was hampered by solubility issues and required extensive optimization to achieve adequate conversions. The final process involved the addition of an excess of mesyl chloride to a warm DMF solution of **5** at high dilution with diisopropylamine as the base. The diisopropylamine also served as a scavenger for the excess mesyl chloride. Final product **1** was isolated in >90% yield by the addition of dilute ammonia to the reaction mixture, providing crystalline material of 99+% purity (Scheme 5).

The process described above has been used on pilot plant scale to provide **1** in the longest linear sequence of seven steps from commercially available materials, in an overall yield of 55%.

Experimental Section

Reactions were carried out under an atmosphere of dry nitrogen. Reagents and solvents were used as received from commercial sources. All reactions were monitored by HPLC analysis using a Symmetry Shield RP-8, 250 × 4.6 mm, 5 μL injection, UV detection at 220 nm, mobile phase A/B: MeCN/(0.1% H_3PO_4 in water, pH adjusted to 6.3−6.4 by NaOH). Flow rate1.5 mL/min. Initial conditions 45% A for 5 min, then ramp to 80% A in 2 min, hold 80% A 3 min. The procedures described are on preparative scale; however, the protocols are applicable to laboratory-scale reactions without modification.

***tert*-Butyl 5-{[4-(*tert*-Butoxycarbonyl)piperazin-1-yl]-methyl}-1*H*-indole-1-carboxylate (2).** To a solution of toluene (8 L), 5-cyanoindole (2 kg, 14 mol), and DMAP (17 g, 0.14

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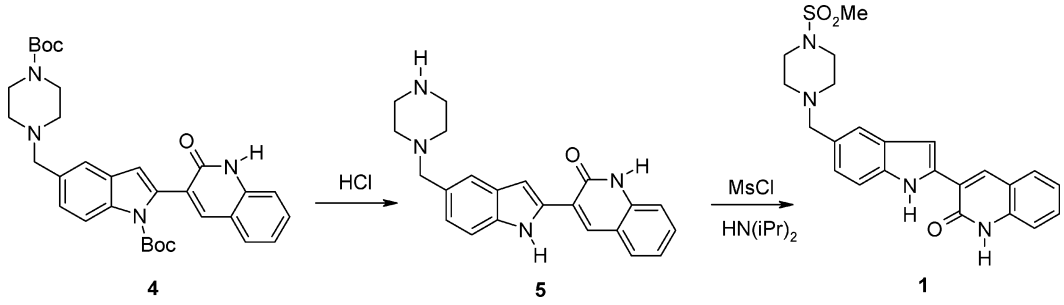
SCHEME 4

SCHEME 5



mol) was slowly added Boc_2O (3.15 kg, 14.5 mol) as a solution in toluene (2 L), followed by a THF rinse (8 L), maintaining a temperature of 20−25 °C. After a 30 min age, the mixture was cooled to 15−18 °C and DIBAL (21.5 L, 32.3 mol) was added over 3 h, maintaining a temperature of 15−18 °C. The solution was aged for 1 h, and then the reaction was slowly quenched into 25% aq $NaHSO_4$ (w/w, 40 L) maintaining a temperature of 35−45 °C. The aqueous phase was removed, and the organic layer was washed with a second portion of 25% aq $NaHSO_4$ (40 L) and then was dried (Na_2SO_4) and filtered (4 L toluene rinse). Boc-piperazine was added (2.61 kg, 14 mol), and then sodium triacetoxyborohydride (4.45 kg, 21 mol) was added in portions, maintaining the temperature between 23 and 27 °C. The mixture was aged for 1.5 h and then was quenched by adding 2.5 v/v % acetic acid in water (20 L). The organic phase was washed with water (20 L) and then was solvent switched to MeOH via in vacuo concentration to a target volume of 25 L. The batch was warmed to 30 °C, seeded, and then cooled to rt. After a good seed bed had formed, 60/40 water/methanol (20 L) was added over 1 h, and then the batch was chilled to 5 °C and aged for 1 h. The product was isolated via filtration and dried via a nitrogen purge. A 4.6 kg yield of white **2** (80%) was obtained: mp 104−106 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.95 (1H, d, J = 7.91 Hz), 7.61 (1H, s), 7.48 (1H, s), 7.23 (1H, d, J = 8.28 Hz), 6.64 (1H, s), 3.51 (2H, s), 3.28 (4H, s), 2.47 (4H, s), 1.59 (9H, s), 1.35 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ; 153.8, 149.1, 133.7, 132.2, 130.2, 126.2, 125.4, 121.3, 114.3, 107.4, 83.7, 78.7, 62.0, 52.3, 43.1, 28.0, 27.6. Anal. Calcd for $C_{23}H_{33}N_3O_4$: C, 66.48; H, 8.00; N, 10.11; O, 15.40. Found: C, 66.60; H, 8.10; N, 9.99; O, 15.61.

3-Bromoquinolin-2(1*H*)-one (3). This is a modification of the literature procedure.[7] Methyltrioxorhenium (24 g, 0.10 mol), THF (16 L), and hydrogen peroxide (30−32 wt %, 6.54 kg, 57.7 mol) were combined, and the bright yellow solution was aged at 20 °C for 5−15 min. 3-Bromoquinoline (4.08 kg, 19.2 mol) was charged, and the solution was aged at 20−25 °C for 48−72 h. Ethyl acetate (20 L) was charged to the batch, and the mixture was cooled to 0−5 °C. A 20 wt % aqueous sodium sulfite solution (28.35 kg, 45 mol) was added, maintaining the temperature <30 °C. The batch was warmed to 20−25 °C, and then the aqueous layer was cut. The organic layer was concentrated to 14 L and was flushed with about 14 L ethyl acetate. The batch was diluted to 40 L with ethyl acetate and then was washed with potassium carbonate solution (15 wt %, ∼19 kg). After removal of the aqueous layer, the temperature of the batch was adjusted to 20−25 °C, potassium carbonate solution (15 wt %, 19 kg) followed by *p*-toluenesulfonyl chloride (4 kg, 21 mol) was added, and the batch was aged at 20−25 °C for 15−24 h. The product was collected via filtration and was washed with 1 × 2 L of ethyl acetate and then with 2 × 4 L water. The product was dried via vacuum at 28−30 °C giving 3.5 kg (81%) of 3-bromoquinolinone: mp 265−269 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.12 (1H, s), 8.45 (1H, s), 7.63 (1H, d, J = 7.5 Hz), 7.50 (1H, t, J = 7.5, 6.8 Hz), 7.29 (1H, d, J = 7.9 Hz), 7.18 (1H, d, J = 7.19 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.7, 141.6, 138.1, 130.7, 127.3, 122.3, 119.4, 117.1, 115.2. Anal. Calcd for C_9H_6-BrNO: C, 48.25; H, 2.70; Br, 35.66; N, 6.25; O, 7.14. Found: C, 48.22; H, 2.71; Br, 35.41; N, 6.22; O, 7.50.

***tert*-Butyl 5-{[4-(*tert*-Butoxycarbonyl)piperazin-1-yl]-methyl}-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-indole-1-carboxylate (4).** To a mixture of **2** (3 kg, 7.2 mol), triisopropyl borate (2.5 L, 10.9 mol), and THF (15 L) at 0 °C was added LDA (4.7 L, 2.0 M, 9.4 mol) keeping the temperature below 5 °C. The mixture was aged for 1 h and then was quenched with 2 N HCl (13 L), and the pH was adjusted to ∼7 by adding ammonium hydroxide. The ice bath was removed, and the biphasic solution was stirred 30 min to ensure that all solids had dissolved. The layers were separated, giving the boronic acid in the organic phase. To a mixture of **3** (1.05 kg, 4.7 mol), palladium acetate (5.3 g, 0.023 mol), triphenylphosphine (12.3 g, 0.047 mol), dicyclohexylamine (2.8 L, 14.1 mol), and THF (10.5 L) at 60 °C was added the boronic acid solution over 3 h. After an overnight age at 60 °C, THF (41 L) and Darco G-60 (320 g) were added, and the mixture was aged for 1 h at 40 °C and then filtered and the carbon cake washed with warm THF (3 L). The filtrate was distilled to a volume of 21 L, and then the solution was allowed to cool to 22 °C, whereupon the product **4** crystallized. Heptane (21 L) was added over 1 h, the mixture aged 1 h, and then the product was isolated via filtration and washed with 1:1 heptane/THF (8 L). After drying, the solid was slurred in water (21 L) and then was collected via filtration with a water wash (10 L). After drying at 40 °C in vacuo, 2.3 kg of **4** was obtained (88%): mp 358−360 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.00 (1H, s), 8.01 (1H, s), 7.99 (1H, d, J = 8.5 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.50 (1H, s), 7.48 (1H, d, J = 8.0 Hz), 7.31 (1H, d, J = 8.2 Hz), 7.25 (1H, d, J = 8.6 Hz), 7.22 (1H, t, J = 7.5, 7.6 Hz), 6.72 (1H, s), 3.53 (2H, s), 3.27 (4H, s), 2.29 (4H, s), 1.35 (9H, s), 1.31 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.0, 153.8, 149.2, 138.5, 136.4, 135.8, 135.7, 132.0, 130.3, 128.4, 128.0, 127.8, 125.7, 122.0, 120.9, 119.1, 114.8, 114.0, 109.4, 83.2, 78.7, 62.0, 52.3,

43.3, 28.0, 27.1. Anal. Calcd for $C_{32}H_{38}N_4O_5$: C, 68.80; H, 6.86; N, 10.03; O, 14.32. Found: C, 68.81; H, 6.88; N, 9.87; O, 14.14.

3-[5-(Piperazin-1-ylmethyl)-1*H*-indol-2-yl]quinolin-2(1*H*)-one (5). A slurry of **4** (2.58 kg, 4.6 mol) in absolute ethanol (39 L) was treated with concentrated aq HCl (5.2 L, 62.4 mol). The solution was then heated to 65 °C for 8 h and then was cooled to rt. Compound **5** as the bis-HCl salt was collected by filtration, with an ethanol (5 L) wash. The product was dried at 50 °C yielding 2.05 kg of **5** (97%): mp 200−201 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.21 (1H, s), 11.86 (1H, s), 9.88 (1H, s), 8.63 (1H, s), 7.84 (1H, s), 7.73 (1H, d, J = 7.7 Hz), 7.60 (1H, d, J = 8.4 Hz), 7.53 (1H, t, J = 0.99, 7.2, 7.2, 1.0 Hz), 7.41 (1H, d, J = 9.1 Hz), 7.38 (1H, s), 7.25 (1H, t, J = 7.4, 7.8 Hz), 4.45 (2H, s), 3.48 (4H, s), 3.43 (4H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.5, 137.7, 136.9, 134.9, 134.7, 130.3, 127.9 (s, 2C), 125.0, 123.9, 122.4, 122.2, 119.4 (s, 2C), 115.0, 112.0, 102.3, 59.5, 46.9, 39.7; exact mass calcd for $C_{22}H_{22}N_4O$ 359.1891 (M + H), found 359.1890.

3-[5-[[4-(Methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indole-2-yl]quinolin-2(1*H*)-one (1). A mixture of **5** (1.5 kg, 3.48 mol), DMF (60 L), and diisopropylamine (1.95 L, 13.9 mol) was heated to 40−45 °C. Methanesulfonyl chloride (600 g, 5.2 mol) in DMF (3 L) was added over 60 min, with a 750 mL DMF rinse. The product crystallized, and the mixture was cooled to 20−25 °C. Dilute ammonium hydroxide (750 mL of concd NH_4OH diluted to 15 L) was added over 1 h. The resulting slurry was aged for 1 h, filtered, and washed with 30% dilute ammonia/DMF (4.5 L), dilute ammonia (4.5 L), water (4.5 L), and ethanol (9 L). The yellow solid was dried in vacuo with a good nitrogen sweep at 70 °C to give 1.36 kg (91.4%) of **1**: mp 275−277 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.15 (1H, s), 11.53(1H, s), 8.52 (1H, 1), 7.73 (1H, d, J = 7.6 Hz), 7.51 (1H, dd, J = 1.0, 7.2, 1.1, 4.3 Hz), 7.46 (1H,s), 7.38 (1H, d, J = 8.2 Hz), 7.29 (1H, d, J = 1.1 Hz), 7.24 (1H, t, J = 7.6, 7.2, 0.58 Hz), 7.08 (1H, d, J = 9.1 Hz), 3.53 (2H, s), 3.07 (4H, s), 2.82 (3H, s), 2.47 (4H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.6, 137.5, 135.9, 133.9, 133.8, 130.1, 128.4, 127.8, 127.8, 123.5, 122.5, 122.3, 120.5, 119.4, 114.9, 111.4, 102.0, 62.3, 51.7, 45.5, 33.6. Anal. Calcd for $C_{23}H_{24}N_4O_3S$: C, 63.28; H, 5.54; N, 12.83; O, 11.0; S, 7.35. Found: C, 62.99; H, 5.56; N, 12.68; O, 11.28, S, 7.02.

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