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

Table of Content

General.................................................................S1
2-Nitro-5-(2-piperidin-1-yloxy)benzaldehyde (26b) ........................................S2
1-{2-[3-(2,2-Dibromovinyl)-4-nitrophenoxy]-ethyl}-piperidine (28b).....................S3
2-(2,2-Dibromovinyl)-4-(2-piperidin-1-yloxy)phenylamine (29b) ....................S3
2-Methoxy-3-[5-(2-piperidin-1-yloxy)-1H-indol-2-yl]quinoline (30b) .................S4
3-[5-(2-Piperidin-1-yloxy)-1H-indol-2-yl]-1H-quinolin-2-one (3) .................S4
5-{2-[2-Methoxyethyl]-methylamino}-ethoxy]-2-nitrobenzaldehyde (26c)..........S5
{2-[3-(2,2-Dibromovinyl)-4-nitrophenoxy]-ethyl}-(2-methoxyethyl)-methylamine (28c) .................................................................S6
2-(2,2-Dibromovinyl)-4-{2-[2-methoxyethyl]-methylamino}-ethoxy]-phenylamine (29c) .................................................................S6
(2-Methoxyethyl)-{2-[2-(methoxyquinolin-3-yl)-1H-indol-5-yl]oxy}-ethyl}-methylamine (30c) .........................................................S7
3-(5-{2-[2-(Methoxyethyl)-methylamino]-ethoxy}-1H-indol-2-yl)-1H-quinolin-2-one (4) .................................................................S8

1 H NMR and 13 CNMR spectra.................................................................S9

General

All flasks were flame-dried under a stream of nitrogen or argon and cooled before use unless otherwise noted. Solvents and solutions were transferred with syringes or cannulae using standard inert atmosphere techniques.

1H and 13C NMR spectra were obtained using a Varian Mercury-300, Gemini-300, Unity-400, Mercury 400, or Unity-500 spectrometer. 1H NMR spectra were referenced to tetramethylsilane (TMS, 0 ppm) using CDCl3 as solvent, DMSO-D5 residue peaks (2.50 ppm) using DMSO-d6 as solvent. 13C NMR spectra were referenced to solvent carbons (77.23 ppm for CDCl3; 39.57 ppm for DMSO-d6). When carbons are equivalent, no special notation is used.
Melting points were taken on a Fisher-Johns melting point apparatus without correction. IR spectra were obtained using a Nicolet DX FT IR spectrometer using thin films of products coated on NaCl plates. Only absorption frequencies higher than 1000 cm\(^{-1}\) are reported. High-resolution mass spectra were obtained from a VG 70-250S (double focusing) mass spectrometer at 70 eV.

Analytical TLC was performed using EM Separations pre-coated silica gel 0.2 mm layer UV 254 fluorescent sheets. Column chromatography was carried out as “flash chromatography” as reported by Still on Ultra Pure Silica Gel (Silicycles, 230-400 mesh, 60A) silica gel using the indicated eluent.\(^1\) Unless otherwise specified, extracts were dried over MgSO\(_4\) and volatile solvents were removed with a rotary evaporator at aspirator pressure.

**2-Nitro-5-(2-piperidin-1-ylethoxy)benzaldehyde (26b)**

![Chemical Structure](image_url)

To a 10-mL round-bottomed flask was charged with 5-hydroxy-2-nitrobenzaldehyde (0.501 g, 3 mmol), 1-(2-chloroethyl)piperidine hydrochloride (0.828 g, 4.5 mmol), and K\(_2\)CO\(_3\) (1.25 g, 9 mmol). After purged with argon for 5 min, anhydrous DMF (3 mL) was added and the mixture was heated at 45 °C overnight (16 h). The mixture was poured into 1 M NaOH (5 mL), extracted with Et\(_2\)O (3× 20 mL), washed with NaHCO\(_3\) (10 mL), H\(_2\)O (10 mL), brine (10 mL), and dried over Na\(_2\)SO\(_4\). The crude material was purified using flash chromatography (3% Et\(_3\)N, 32% EtOAc and 65% hexanes) to afford the product was a slight yellow oil (0.710 g, 85%).\(^1\)\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 10.48 (1H, s), 8.15 (1H, d, J = 9.0 Hz), 7.34 (1H, d, J = 2.9 Hz), 7.16 (1H, dd, J = 9.0, 2.9 Hz), 4.23 (2H, t, J = 5.8 Hz), 2.81 (2H, t, J = 5.9 Hz), 2.50 (4H, t, J = 5.1 Hz), 1.61 (4H, quintet, J = 5.7 Hz), 1.45 (2H, quintet, J = 5.6 Hz).

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1-{2-[3-(2,2-Dibromovinyl)-4-nitrophenoxy]-ethyl}-piperidine (28b)

To a solution of the aldehyde (0.174 g, 0.625 mmol) and CBr₄ (0.311 g, 0.94 mmol) in DCM (3 mL) was added a solution of PPh₃ (0.493 g, 1.88 mmol) in DCM (1 mL) at 0 °C. The mixture was stirred for 30 min, warmed to rt, and quenched with NaHCO₃ (5 mL). The mixture was extracted with Et₂O (15 mL) and EtOAc (15 mL), washed with brine, and dried over Na₂SO₄. The crude material was purified by flash chromatography to afford 28b as a slightly yellow oil (0.2156 g, 79%). ¹H NMR (500 MHz, CDCl₃) δ 8.15 (1H, d, J = 9.1 Hz), 7.84 (1H, d, J = 0.5 Hz), 7.02 (1H, d, J = 2.7 Hz), 6.97 (1H, J = 9.1, 2.7 Hz), 4.20 (2H, t, J = 7.5 Hz), 2.80 (2H, t, J = 6.0 Hz), 2.51 (4H, t, J = 5.0 Hz), 1.61 (4H, quintet, J = 5.7 Hz), 1.46 (2H, quintet, J = 5.8 Hz). ¹³C NMR (125 MHz, CDCl₃) δ 162.9, 140.1, 134.9, 134.1, 127.6, 117.1, 115.3, 92.8, 67.5, 57.8, 55.4, 26.2, 24.3. HRMS calc’d for C₁₅H₁₉N₂O₃Br₂ ([M+H]⁺) 432.9756. Found: 432.9770.

2-(2,2-Dibromovinyl)-4-(2-piperidin-1-ylethoxy)phenylamine (29b)

A mixture of the nitrobenzene (0.215 g, 0.495 mmol) and 1% Pt-C[V] (26 mg) in MeOH (5 mL) was hydrogenated at 25 psi for 3 h using a Parr hydrogenator. After removal of the catalyst through filtration, the solvent was evaporated to give 29b as a colorless oil (0.189 g, 94%). IR (neat, cm⁻¹): 3431, 3361, 2933, 1611, 1497, 1262, 1222, 1164, 1040. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (1H, s), 6.91 (1H, d, J = 2.9 Hz), 6.78 (1H, dd, J = 8.6, 2.9 Hz), 6.65 (1H, d, J = 8.6 Hz), 4.08 (2H, t, J = 5.9 Hz), 3.49 (3H, s), 3.45 (2H, br), 2.80 (2H, t, J = 5.9 Hz), 2.56 (4H, br), 1.68-1.62 (4H, m), 1.49-1.46 (2H, m). ¹³C NMR (100 MHz, CDCl₃) δ 151.6, 137.7, 134.1, 122.8, 117.4, 117.2, 114.9, 92.7,
To a 5 mL round-bottomed flask was charged with aniline 29b (0.0818 g, 0.202 mmol), boronic acid 13 (0.0616 g, 0.30 mmol), Pd(OAc)$_2$ (2.2 mg, 0.01 mmol), S-Phos (8.2 mg, 0.02 mmol), and K$_3$PO$_4$·H$_2$O (0.184 g, 0.8 mmol). After the flask was purged with argon for 10 min, PhMe (5 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was then quenched with NaHCO$_3$, extracted with EtOAc (3 × 10 mL), and dried over Na$_2$SO$_4$. The crude material was purified by flash chromatography using 33% EtOAc in hexanes containing 3% $i$PrNH$_2$ to afford the product 30b as a slightly solid (0.0531 g, 65%). mp 134-136 ºC. IR (neat, cm$^{-1}$): 3457, 2935, 1621, 1475, 1249, 1193. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.55 (1H, br), 8.41 (1H, s), 7.84 (1H, dd, $J = 7.1, 0.8$ Hz), 7.75 (1H, dd, $J = 7.9, 1.3$ Hz), 7.60 (1H, ddd, $J = 8.2, 7.0, 1.5$ Hz), 7.40 (1H, ddd, $J = 7.9, 7.0, 1.3$ Hz), 7.32 (1H, d, $J = 8.8$ Hz), 7.11 (1H, d, $J = 2.4$ Hz), 6.98 (1H, dd, $J = 2.2, 0.9$ Hz), 6.89 (1H, dd, $J = 8.8, 2.4$ Hz), 4.26 (3H, s), 4.18 (2H, t, $J = 6.2$ Hz), 2.81 (2H, t, $J = 6.1$ Hz), 2.54 (4H, br), 1.62 (4H, quintet, $J = 5.7$ Hz), 1.45 (2H, quintet, $J = 6.1$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.4, 153.8, 145.3, 135.1, 134.2, 132.0, 129.6, 128.8, 127.6, 127.1, 125.7, 125.0, 116.9, 113.9, 112.1, 103.1, 101.1, 66.8, 58.4, 55.3, 54.2, 26.2, 24.5. HRMS calc’d for C$_{25}$H$_{28}$N$_3$O$_2$ ([M+H]$^+$) 402.2176. Found: 402.2181.
A mixture of 30b (38 mg, 0.0946 mmol) and HCl (3 mL, 3 M) was heated to 90 °C overnight. Solid K₂CO₃ was carefully added to the mixture until it is neutral, and the mixture was filtered through a Celite pad (0.2 g). The crude material on celite was washed with sufficient amounts of water and dried under vacuum. The solid was wrapped in a filter paper and loaded in a thimble, and extracted with a Soxlet extractor using a mixed solvent of DCM and MeOH. The resulting solution was concentrated to ~3 mL, and the residual solvent was carefully removed with a pipette. After washed with DCM (2 mL), the product was dried under vaccum as a yellow solid (33.6 mg, 92%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.63 (1H, s), 8.51 (1H, s), 7.71 (1H, d, J = 7.7 Hz), 7.48 (1H, t, J = 7.4 Hz), 7.41 (1H, d, J = 8.8 Hz), 7.37 (1H, d, J = 8.1 Hz), 7.21 (1H, t, J = 7.5 Hz), 7.19 (1H, s), 7.06 (1H, s), 6.75 (1H, dd, J = 8.6, 2.1 Hz), 4.05 (2H, t, J = 5.8 Hz), 2.66 (2H, t, J = 5.8 Hz), 2.44 (4H, br), 1.50 (4H, m), 1.38 (2H, m). ¹³C NMR (100 MHz, CDCl₃) δ 161.0, 152.7, 138.1, 134.4, 133.5, 131.7, 129.8, 128.3, 127.7, 122.3, 122.0, 119.6, 115.3, 112.8, 112.4, 102.3, 101.4, 66.0, 57.7, 54.5, 25.6, 24.0. HRMS (ESI) calc'd for C₂₄H₂₆N₃O₂ ([M+H]⁺) 388.2019. Found: 388.2023.

5-{2-[2-(2-Methoxyethyl)-methylamino]-ethoxy}-2-nitrobenzaldehyde (26c)

(2-Chloroethyl)-(2-methoxyethyl)-methylamine 27c was prepared by neutralization of its hydrochloride, which was prepared according the literature procedure. ² To a 10-mL round-bottomed flask was charged with 5-hydroxy-2-nitrobenzaldehyde (1.28 g, 7.6 mmol), 2-chloroethyl)-(2-methoxyethyl)-methylamine (1.51 g, 10 mmol), and K₂CO₃ (2.2 g, 15 mmol). After purged with argon for 5 min, anhydrous DMF (5 mL) was added

and the mixture was heated at 70 ºC for 6 h. The mixture was poured into 1 M NaOH (5 mL), extracted with Et₂O (3×20 mL), washed with NaHCO₃ (10 mL), H₂O (10 mL), brine (10 mL), and dried over Na₂SO₄. The crude material was purified using flash chromatography (5% Et₃N, 50% EtOAc and 50% hexanes) to afford the product was a slight yellow oil (1.01 g, 47%). IR (neat, cm⁻¹): 2881, 1694, 1585, 1515, 1332, 1289, 1243, 1119, 1073, 1025. ¹³C NMR (100 MHz, CDCl₃) δ 188.7, 163.5, 142.4, 134.5, 127.4, 119.2, 114.0, 70.7, 67.7, 59.1, 57.4, 56.3, 43.5. HRMS (ESI) calc’d for C₁₃H₁₉N₂O₅ ([M+H]^+) 283.1288. Found: 283.1283.

{2-[3-(2,2-Dibromovinyl)-4-nitrophenoxy]-ethyl}-(2-methoxyethyl)-methylamine (28c)

To a solution of the aldehyde 26c (0.384 g, 1.36 mmol) and CBr₄ (0.681 g, 2.05 mmol) in DCM (5 mL) was added a solution of PPh₃ (1.074 g, 4.1 mmol) in DCM (2 mL) at 0 ºC. The mixture was stirred for 30 min, warmed to rt, and quenched with NaHCO₃ (5 mL). The mixture was extracted with Et₂O (15 mL) and EtOAc (15 mL), washed with brine, and dried over Na₂SO₄. The crude material was purified by flash chromatography to afford 28c as a slightly yellow oil (0.480 g, 81%). IR (neat, cm⁻¹): 2879, 1577, 1464, 1335, 1293, 1236, 1118, 1082. ¹H NMR (500 MHz, CDCl₃) δ 8.16 (1H, d, J = 9.2 Hz), 7.79 (1H, s), 7.01 (1H, d, J = 2.8 Hz), 6.97 (1H, J = 9.2, 2.8 Hz), 4.19 (2H, t, J = 5.9 Hz), 3.51 (2H, t, J = 5.6 Hz), 3.36 (3H, s), 2.92 (2H, t, J = 5.8 Hz), 2.71 (2H, t, J = 5.6 Hz), 2.41 (3H, s). ¹³C NMR (125 MHz, CDCl₃) δ 162.8, 139.9, 135.0, 134.1, 127.7, 117.0, 115.2, 92.8, 70.7, 67.5, 59.2, 57.6, 56.4, 43.5. HRMS (ESI) calc’d for C₁₄H₁₉N₂O₄Br₂ ([M+H]^+) 436.9706. Found: 436.9717.

2-(2,2-Dibromovinyl)-4-{2-[2-methoxyethyl]-methylamino}-ethoxy}-phenylamine (29c)
A mixture of the nitrobenzene 28c (0.465 g, 1.06 mmol) and 1% Pt-C[V] (50 mg) in MeOH (5 mL) was hydrogenated at 25 psi for 4 h using a Parr hydrogenator. After removal of the catalyst and solvent, the compound was purified by flash chromatography to give 29c as a colorless oil (0.380 g, 88%). IR (neat, cm⁻¹): 3437, 3349, 3222, 2874, 1610, 1496, 1259, 1227, 1166, 1117, 1044. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (1H, s), 6.91 (1H, d, J = 2.7 Hz), 6.77 (1H, dd, J = 8.6, 3.0 Hz), 6.63 (1H, d, J = 8.6 Hz), 4.02 (2H, t, J = 6.0 Hz), 3.50 (2H, t, J = 5.7 Hz), 3.45 (2H, br), 3.35 (3H, s), 2.83 (2H, t, J = 6.0 Hz), 2.69 (2H, t, J = 5.8 Hz), 2.39 (3H, s). ¹³C NMR (100 MHz, CDCl₃) δ 151.7, 137.7, 134.1, 122.8, 117.4, 117.2, 114.9, 92.7, 70.8, 67.0, 59.0, 57.4, 56.8, 43.5. HRMS calc’d for C₁₄H₂₁N₂O₂Br₂ ([M+H]⁺) 406.9964. Found: 406.9977.

(2-Methoxyethyl)-{2-[2-(2-methoxyquinolin-3-yl)-1H-indol-5-yloxy]-ethyl}methylamine (30c)

To a 5 mL round-bottomed flask was charged with aniline 29c (0.122 g, 0.3 mmol), boronic acid 13 (0.0914 g, 0.45 mmol), Pd(OAc)₂ (3.4 mg, 0.015 mmol), S-Phos (12.3 mg, 0.03 mmol), and K₃PO₄·H₂O (0.345 g, 1.5 mmol). After the flask was purged with argon for 10 min, PhMe (1.5 mL) was added was and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was then quenched with NaHCO₃, extracted with EtOAc (3 × 10 mL), and dried over Na₂SO₄. The crude material was purified by flash chromatography using 33% EtOAc in hexanes containing 3% iPrNH₂ to afford the product 30c as a slightly yellow oil (0.0832 g, 68%). IR (neat, cm⁻¹): 1456, 2943, 1622, 1475, 1398, 1194, 1118. ¹H NMR (400 MHz, CDCl₃) δ 9.54 (1H, br), 8.41 (1H, s), 7.84 (1H, d, J = 8.2 Hz), 7.75 (1H, dd, J = 8.0, 1.1 Hz), 7.60 (1H, ddd, J = 8.3, 7.1, 1.4 Hz),
7.40 (1H, ddd, \( J = 7.5, 7.5, 1.0 \) Hz), 7.32 (1H, d, \( J = 8.8 \) Hz), 7.10 (1H, d, \( J = 2.3 \) Hz), 6.98 (1H, dd, \( J = 1.6 \) Hz), 6.89 (1H, dd, \( J = 8.8, 2.3 \) Hz), 4.26 (3H, s), 4.16 (2H, t, \( J = 6.0 \) Hz), 3.53 (2H, t, \( J = 5.7 \) Hz), 3.37 (3H, s), 2.91 (2H, t, \( J = 6.0 \) Hz), 2.73 (2H, t, \( J = 5.6 \) Hz), 2.43 (3H, s). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 158.4, 153.8, 145.3, 135.1, 134.2, 131.9, 129.6, 128.8, 127.6, 127.1, 125.7, 125.0, 116.9, 113.9, 112.1, 103.0, 101.1, 70.9, 66.9, 59.1, 57.4, 57.0, 54.2, 43.5. HRMS calc’d for C\(_{24}\)H\(_{28}\)N\(_3\)O\(_3\) ([M+H]\(^+\)) 406.2125. Found: 406.2130.

3-(5-{2-[(2-Methoxyethyl)-methylamino]-ethoxy}-1H-indol-2-yl)-1H-quinolin-2-one

\( 4 \)

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{Me} \\
\text{O} & \quad \text{N} & \quad \text{Me} & \quad \text{O} \\
\text{O} & \quad \text{N} & \quad \text{Me} & \quad \text{O} \\
\text{N} & \quad \text{Me} & \quad \text{O} & \quad \text{Me}
\end{align*}
\]

A mixture of 30c (41 mg, 0.101 mmol) and HCl (2 mL, 3 M) was heated to 90 °C overnight. Solid K\(_2\)CO\(_3\) was carefully added to the mixture until it is neutral, and the mixture was filtered through, and the collected product was washed with H\(_2\)O and dried under vacuum to afford 4 as a yellow solid (35.4 mg, 90%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 11.32 (1H, br), 11.07 (1H, s), 8.27 (1H, s), 7.61 (1H, d, \( J = 7.6 \) Hz), 7.46 (1H, ddd, \( J = 7.7, 7.7, 1.1 \) Hz), 7.35 (1H, d, \( J = 8.8 \) Hz), 7.28-7.23 (2H, m), 7.09 (1H, d, \( J = 2.2 \) Hz), 6.94 (1H, d, \( J = 1.4 \) Hz), 6.90 (1H, dd, \( J = 8.8, 2.3 \) Hz), 4.17 (2H, t, \( J = 6.1 \) Hz), 3.55 (2H, t, \( J = 5.7 \) Hz), 3.38 (3H, s), 2.93 (2H, t, \( J = 6.0 \) Hz), 2.75 (2H, t, \( J = 5.8 \) Hz), 2.45 (3H, s). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 163.1, 153.8, 136.9, 134.8, 134.7, 131.9, 130.5, 128.5, 128.1, 123.6, 122.3, 120.7, 115.5, 114.1, 112.6, 102.7, 99.4, 70.9, 66.9, 59.1, 57.5, 57.0, 43.5. HRMS (ESI) calc’d for C\(_{23}\)H\(_{26}\)N\(_3\)O\(_2\) ([M+H]\(^+\)) 392.1968. Found: 392.1983.
benzyl alcohol intermediate