Supporting Information

2-(Quinazolin-4-ylamino)-[1,4]benzoquinones are Covalent Binding Irreversible Inhibitors of the Kinase Domain of Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2, also known as KDR).

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Additional syntheses and spectral data

***N*-(3,4-Dichloro-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinazolin-4-amine (8b)**. This compound was prepared from **6** (6.4 g, 23.08 mmol), the hydrochloride salt of **7b** (6.56 g, 25.38 mmol), and NaOAc (2.08 g, 25.38 mmol) using the method described above for **8a** to yield 3.9 g of **8b** as a white solid (37%): MS (ESI) *m/z* 454.1 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-D_6) δ 3.25-3.41 (m, 3 H), 3.64 (s, 3 H), 3.69-3.79 (m, 2 H), 3.85 (s, 3 H), 3.96 (s, 3 H), 4.20-4.36 (m, 2 H), 7.21 (s, 1 H), 7.41 (s, 1 H), 7.90 (s, 1 H), 8.37 (s, 1 H), 9.54 (s, 1 H).

2,3-Dichloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (9b). This compound was prepared from **8b** (3.8 g, 8.36 mmol) using the procedure described above for **9a** to give **9b** (1.85 g of a red solid) in 52% yield: MS (ESI) *m/z* 424.1 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.79-3.97 (m, 2 H,), 4.07 (s, 3 H,), 4.25-4.41 (m, 2 H), 7.02 (s, 1 H), 7.33 (s, 1 H), 8.34 (s, 1 H), 8.57 (s, 1 H), 8.84 (s, 1 H); HRMS (ESI-FTMS $(M+H)^{+1}$) calcd for $C_{18}H_{15}Cl_2N_3O_5$, 424.04615; found, 424.04622. The purity of **9b** was evaluated by two HPLC systems and found to be 99 % (system A, retention time = 8.04 min) and 98 % (system B, retention time = 14.9 min).

***N*-(4-Chloro-2,3,5-trimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy) quinazolin-4-amine (8e).** A solution of **6** (7.8 g, 28.13 mmol) and **7e** (6.12 g, 28.13 mmol) in AcOH (246 ml) was refluxed for 3.5 h. The reaction was cooled to rt and diluted with ether. The resulting solid was collected by filtration to yield 12.03 g of **8e** as a beige powder (95%): MS (ESI) *m/z* 450.1 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-D_6) δ 3.34 (s, 3 H), 3.68 (s, 3 H), 3.72-3.77 (m, 2 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 4.23-4.30 (m, 2 H), 7.17 (s, 1 H), 7.20 (s, 1 H), 7.83 (s, 1 H), 8.37 (s, 1 H), 9.30 (s, 1 H).

2-Chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (9e). Compound **8e** (1.0 g, 2.22 mmol) was boiled in CH_3CN (20 ml) until dissolved and H_2O (2 mL) was added. While still hot the solution was treated with CAN (2.86 g, 5.22 mmol) in portions over 2 min. The reaction was then stirred at rt for 1 h, diluted with H_2O (300 mL), and extracted with $CHCl_3$ (5 x 800 ml). The organic solution was dried (Na_2SO_4) and filtered through a pad of magnesol (eluting with CH_3Cl-EtOAc). The solvent was removed at reduced pressure. The resulting solid was dissolved in boiling CH_3CN (200 mL) and diluted with ether (200 mL). A red solid formed upon cooling and was collected by filtration to give 0.59 g (63 %) of **9e**: MS (ESI) *m*/*z* 420 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.82-3.95 (m, 2 H), 4.08 (s, 3 H), 4.20 (s, 3 H), 4.26-4.40 (m, 2 H), 7.03 (s, 1 H), 7.32 (s, 1 H), 8.20 (s, 1 H), 8.47 (s, 1 H), 8.81 (s, 1 H). Anal. ($C_{19}H_{18}ClN_3O_6 \cdot 0.5\ H_2O$) C, H, N.

***N*-(2,5-Dimethoxy-4-methylphenyl)-6-methoxy-7-(2-methoxyethoxy) quinazolin-4-amine (8f)**. A mixture of **6** (5.55 g, 0.02 mmol) and 2,4,5-trimethoxyaniline (3.68 g, 0.022 mmol) in 50 mL of HOAc was refluxed at 139 °C for 1 h. The reaction was cooled to rt. The resulting solid was filtered and washed with ether to give 4.9 g (62.2 %) of **8f** as a yellow solid: mp 165-168 °C; MS (ESI) *m*/*z* 400.2 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (s, 3 H), 2.20 (s, 3 H), 3.70 (s, 3 H), 3.73-3.75 (m, 5 H), 3.93 (s, 3 H), 4.24 – 4.26 (m, 2 H), 6.95 (s, 1 H), 7.08 (s, 1 H), 7.16 (s, 1 H), 7.80 (s, 1 H), 8.28 (s, 1 H), 9.11 (s, 1 H).

2-{[6-Methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-5-methylbenzo-1,4-quinone (9f). A solution of **8f** (3.0 g, 7.51 mmol) in 100 mL CH_3CN was prepared by heating. H_2O (13 mL) was added to the warm mixture followed by 9.06 g (16.52 mmol) of CAN over 15 min. The reaction mixture was stirred at rt for 1.5 h. The mixture was poured into CH_2Cl_2 and washed with H_2O and brine. The organic layer was separated and dried over $MgSO_4$. The solution was passed through a short magnesol column, eluting with CH_2Cl_2 and then CH_2Cl_2-isopropanol (9:1). The solvent was removed from the filtrate and the residue was stirred with CH_3CN/ether. The resulting solid was collected to yield 2.2 g (79.3 %) of **9f** as a red crystalline solid: HRMS (ESI-FTMS, $(M+H)^{+1}$): calcd for $C_{19}H_{19}N_3O_5$, 370.13975; found, 370.14173; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 3 H), 3.34 (s, 3 H), 3.74-3.76 (m, 2 H), 4.01 (s, 3 H), 4.30-4.32 (m, 2 H), 6.89 (s, 1 H), 7.33 (s, 1 H), 7.56 (s, 1 H), 7.79 (s, 1 H), 8.76 (s, 1 H), 9.09 (bs, 1 H); Anal.($C_{19}H_{19}N_3O_5.1.1\ H_2O$) N, H, C: calcd, 58.07; found, 58.64.

***N*-(2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinazolin-4-amine (8g)**. A solution of **6** (5.63 g, 20.3 mmol) and 2,5-dimethoxyaniline (3.42 g, 22.33 mmol) in 24 mL of HOAc was refluxed for 1 h. The reaction was diluted with ether. The solid was collected and recrystallized from isopropanol to yield 6.45 g (82.4 %) of **8g** as grey solid: MS (ESI) *m*/*z* 386.2 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.34 (s, 3 H), 3.73 (m, 8 H), 3.94 (m,3 H), 4.24-4.27 (m, 2 H), 6.80 (dd, J = 8.94, 3.15 Hz, 1 H), 7.04 (d, J = 8 Hz, 1 H), 7.17 (s, 1 H), 7.20 (d, J = 3.02 Hz, 1 H), 7.79 (s, 1 H), 8.32 (s, 1 H), 9.09 (s, 1 H); Anal. ($C_{25}H_{23}N_3O_6$) C, H, N.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (9g). To a solution of **8g** (6.2 g, 16.09 mmol) in 202 mL of warm CH_3CN was added 30 mL of H_2O and CAN (26.46 g, 48.26 mmol) portion wise over 40 min. The reaction was stirred for 30 min. It was poured into 800 mL CH_2Cl_2 and washed twice with H_2O. The organic layer was dried over $MgSO_4$ and filtered through a pad of magnesol, eluting with EtOAc. The solvent of the product fraction was evaporated in vacuo. The residue was recrystallized from CH_3CN-ether to yield 2.67 g (46.7 %) of **9g** as an orange solid: MS (ESI) *m*/*z* 356 $(M+H)^{+1}$; HRMS (ESI-FTMS, $(M+H)^{+1}$): calcd for $C_{18}H_{17}N_3O_5$, 356.12410; found, 356.12452; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.90 (m, 2 H), 4.07 (s, 3 H), 4.33-4.35 (m, 2 H), 6.81 (dd, *J* = 4 Hz, *J* = 12 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 1 H), 7.04 (s, 1 H), 7.32 (s, 1 H), 8.14 (d, *J* = 2.52 Hz, 1 H), 8.46 (s, 1 H), 8.81 (s, 1 H); Anal.($C_{18}H_{17}N_3O_5$.0.66 H_2O) C, H, N.

6-Methoxy-7-(2-methoxyethoxy)-*N*-(2,4,5-trimethoxyphenyl)quinazolin-4-amine (8h). A mixture of **6** (8.0 g, 28.85 mmol) and 2,3,5-trimethoxyaniline (5.81 g, 31.73 mmol) in 35 mL HOAc was stirred at reflux for 1 h. The mixture was cooled to rt, diluted with 550 mL ether and stirred for 1 h. The solid was collected and washed with ether giving 9.05 g (75.5 %) of **8h** as a tan crystalline solid: MS (ESI) *m*/*z* 416.1 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.34 (s, 3 H), 3.59 (s, 3 H), 3.73-3.75 (m, 5 H), 3.84 (s, 3 H), 3.94 (s, 3 H), 4.23-4.29 (m, 2 H), 6.54 (d, *J* = 3.02 Hz, 1 H), 6.75 (d, *J* = 3.02 Hz, 1 H), 7.18 (s, 1 H), 7.80 (s, 1 H), 8.34 (s, 1 H), 9.16 (s, 1 H); Anal. ($C_{21}H_{27}N_3O_6$.0.1 H_2O) C, H, N.

***N*-(3-Bromo-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinazolin-4-amine (8k)**. A mixture of **6** (7.37 g, 26.58 mmol) and 3-bromo-2,5-dimethoxy-aniline (6.1 g, 27.97 mmol) in 33 mL of HOAc was refluxed for 1 h 15 min. The reaction was cooled, poured into H_2O and neutralized with 5 *N* NaOH. The solid was collected, washed with H_2O and air-dried. The residue was recrystallized from EtOAc-hexanes to yield 9.3 g (75.3 %) of **8k**: MS (ESI) *m*/*z* 464.1 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.34 (s, 3 H), 3.60 (s, 3 H), 3.74-3.76 (m, 5 H), 3.95 (s, 3 H), 4.26-4.28 (m, 2 H), 7.09 (d, *J* = 4 Hz, 1 H), 7.21 (s, 1 H), 7.25 (d, *J* = 3.02 Hz, 1 H), 7.84 (s, 1 H), 8.38 (s, 1 H), 9.35 (s, 1 H).

2-Bromo-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (9k). To a warm solution of **8k** (8.9 g, 19.17 mmol) in 436 mL of CH_3CN at 50 ^oC was added 87 mL of H_2O and CAN (26.27 g, 47.92 mmol) over 10 min. The reaction was stirred at rt for 1.5 h and heated to 45 ^oC. The reaction was cooled, diluted with 1L CH_2Cl_2, and washed with H_2O. The organic layer was separated and dried over $MgSO_4$. The solution was filtered through a magnesol plug, eluting with $CHCl_3$-EtOAc-isopropanol. The solvent was evaporated. The resulting solid was chromatographed on a silica gel column, eluting with $CHCl_3$-EtOAc (1:1). The solvent of product fractions was evaporated to give 2.4 g (28.8 %) of **9k** as a red solid crystalline: MS (ESI) *m*/*z* 434 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.88-3.90 (m, 2 H), 4.06 (s, 3 H), 4.33-4.35 (m, 2 H), 7.04 (s, 1 H), 7.29 (d, *J* = 2.27 Hz, 1 H), 7.33 (s, 1 H), 8.21 (d, *J* = 2.27 Hz, 1 H), 8.54 (s, 1 H), 8.83 (s, 1 H); Anal. ($C_{18}H_{16}BrN_3O_5$. 0.25 H_2O) C, N, H: calcd, 3.35; found, 3.79.

2-Methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (9h). A sample of **8h** (8.65 g, 20.82 mmol) was oxidized with CAN as described above for **9a** to give 2.27 g (28.3 %) of **9h** as a fibrous crystalline red solid: MS (ESI) *m*/*z* 386.1 $(M+H)^{+1}$; HRMS (ESI-FTMS, $(M+H)^{+1}$): calcd for $C_{19}H_{19}N_3O_6$, 386.13466; found, 386.13594; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.34 (s, 3 H), 3.74-3.76 (m, 2 H), 3.83 (s, 3 H), 4.01 (s, 3 H), 4.29-4.31 (m, 2 H), 6.08 (s, 1 H), 7.31 (s, 1 H), 7.59 (s, 1 H), 7.62 (d, *J* = 2.52 Hz, 1 H), 8.73 (s, 1 H), 9.12 (s, 1 H); Anal. ($C_{19}H_{19}N_3O_6$. 0.33 H_2O) C, H, N.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(methylthio) benzo-1,4-quinone (9l). This compound was prepared from **8l** (130 mg, 0.3 mmol) and CAN (345 mg, 21.0 mmol) in $CHCl_3$ (1.5 mL), CH_3CN (3.0 ml), and H_2O (0.6 mL) using the procedure described above for **9e** to give 102 mg (84%) of **9l** as a red solid: MS (ESI) *m*/*z* 402 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{19}H_{19}N_3O_5S$, 402.11182; found, 402.11222; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 3.49 (s, 3 H), 3.88-3.90 (m, 2 H), 4.08 (s, 3 H), 4.33-4.35 (m, 2 H), 6.39 (s, 1 H), 7.07 (s, 1 H), 7.33 (s, 1 H), 8.14 (s, 1 H), 8.72 (s, 1 H), 8.83 (s, 1 H). The purity of **9r** was evaluated by two HPLC systems and found to be 96 % (system A, retention time = 6.16 min) and 93 % (system B, retention time = 12.78 min).

N-(4-Bromo-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-amine (8m). This compound was prepared from **6** (8.32 g, 30 mmol) and **7m** (7.66 g, 33 mmol) in HOAc (30 ml) using the procedure described above for **8e** to give 12.17 g (87%) of **8m** as a grey solid: mp 217-221 °C; MS (ESI) *m*/*z* 464 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-D_6) δ 3.34 (s, 3 H), 3.71-3.77 (m, 5 H), 3.78-3.80 (m, 3 H), 3.94 (s, 3 H), 4.22-4.28 (m, 2 H), 7.18 (s, 1 H), 7.34 (s, 1 H), 7.37 (s, 1 H), 7.79 (s, 1 H), 8.32 (s, 1 H), 9.18 (s, 1 H).

2-Bromo-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (9m). This compound was prepared from **8m** (300 mg, 0.65 mmol) and CAN (0.78 g, 1.43 mmol) in CH_3CN (8.6 ml) and H_2O (1.1 ml) using the procedure described above for **9e** to give 256 mg (90.6%) of **9m** as a purple red solid: mp 200-210 °C; HRMS (ESI-FTMS, $(M+H)^{+1}$): calcd for $C_{18}H_{16}BrN_3O_5$, 434.03461; found, 434.03449; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.88 – 3.90 (m, 2 H), 4.07 (s, 3 H), 4.33-4.35 (m, 2 H), 7.03 (s, 1 H), 7.40 (s, 1 H), 8.34 (s, 1 H), 8.46 (s, 1 H), 8.83 (s, 1 H). Anal. ($C_{18}H_{16}BrN_3O_5$) C, H, N.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(phenyl) amino] benzo-1,4-quinone (12). Compound **12** was prepared using the same method as described for **11** (Method B) starting from 1.13 g (2.5 mmol) of **9a** and 0.99 g (9.23 mmol) of N-methyl aniline in 10 mL ethylene glycol dimethyl ether. The reaction was heated at 85 ^{o}C for 2 h. The solid was recrystallized in acetic acid and washed with ether to yield 546 mg (47.4%) of **12**: mp 239-243 °C; MS (ESI) m/z 461.2 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{25}H_{24}N_4O_5$, 461.18195; found,

461.18218; the purity of **12** was evaluated by two HPLC systems and found to be 100 % (system C, retention time = 5.49 min) and 89.7% (system D, retention time = 15.40 min); ^{1}H NMR (400 MHz, DMSO-D_6) δ 3.34 (s, 3 H), 3.38 (s, 3 H), 3.73-3.78 (m, 2 H), 4.04 (s, 3 H), 4.31-4.40 (m, 2 H), 5.92 (s, 1 H), 7.21 (d, J = 7.55 Hz, 2 H), 7.27 (t, J = 7.30 Hz, 1 H), 7.37-7.42 (m, 3 H), 7.49-7.52 (m, 1 H), 7.66 (s, 1 H), 8.91 (s, 1 H), 9.68 (d, J = 2.01 Hz, 1 H).

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(4-methoxyphenyl) (methyl)amino]benzo-1,4-quinone (13). Compound **13** was prepared using the same method as described for **11** (Method B) starting from 1.13 g (2.5 mmol) of **9a** and 1.37 g (10.0 mmol) of N-methyl-p-anisidine in 30 mL acetic acid. The reaction was heated at 85 ^{o}C for 2 h yielding 765 mg (62.4%) of **13** as a brown solid: mp 197-198 °C; MS (ESI) m/z 491.3 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, DMSO-D_6) δ 3.34 (s, 3 H), 3.36 (s, 3 H), 3.72-3.77 (m, 2 H), 3.78 (s, 3 H), 4.01 (s, 3 H), 4.25-4.36 (m, 2 H), 5.73 (s, 1 H), 6.96 (d, J = 8.81 Hz, 2 H), 7.15 (d, J = 8.56 Hz, 2 H), 7.32 (s, 1 H), 7.40 (s, 1 H), 7.52 (s, 1 H), 8.74 (s, 1 H), 9.21 (s, 1 H); Anal.($C_{26}H_{26}N_4O_6$. 0.50 H_2O) C, H, N.

2-(Benzyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (15). Compound **15** was prepared using the same method as described for **14** (Method C) starting from 0.673 g (1.504 mmol) of **13**, 20 mL (10.51 mmol) of benzyl alcohol, and 10 drops of Et_3N in 20 mL CH_2Cl_2. In this instance, the reaction was stirred at rt overnight. The CH_2Cl_2 was evaporate in vacuo. The resulting oil was treated with 200 mL of ether. The resulting solid was filtered and washed with ether to yield 0.658 g (94.8%) of **15** as an orange solid: mp 218-220 °C; MS (ESI) m/z 462.4 $(M+H)^{+1}$; ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 3.48 (s, 3 H), 3.82-3.94 (m, 2 H), 4.06 (s, 3 H), 4.26-4.39 (m, 2 H), 5.14 (s, 2 H), 6.04 (s, 1 H), 7.04 (s, 1 H), 7.26 (s, 1 H), 7.31 (s, 1 H), 7.34-7.47 (m, 4 H), 8.06 (s, 1 H), 8.71 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{25}H_{23}N_3O_6$. 0.25 H_2O) C, H, N.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-piperidin-1-ylbenzo-1,4-quinone (17). Compound **17** was prepared using the same method as described for **11** (Method B) starting from 200 mg (0.51 mmol) of **9a**, 175 mg (2.04 mmol) of piperidine and pyridine hydrochloride (59 mg, 0.51 mmol) in 4 mL THF. In this instance, the reaction was stirred at rt for 3 h. The product was recrystallized from CH_3CN-CH_2Cl_2 to yield 78 mg (35%) of **17** as a brown solid: mp 197-200 °C; MS (ESI) *m/z* 439.3 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{23}H_{26}N_4O_5$, 439.19760; found, 439.19608; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.82 (m, 6 H), 3.48 (s, 3 H), 3.62-3.73 (m, 4 H), 3.83-3.94 (m, 2 H), 4.06 (s, 3 H), 4.25-4.42 (m, 2 H), 5.77 (s, 1 H), 7.12 (s, 1 H), 7.29-7.36 (m, 1 H), 7.79 (s, 1 H), 8.82 (s, 1 H), 9.08 (s, 1 H); Anal. ($C_{23}H_{26}N_4O_5$) C, H, N.

2-(3-Fluorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (19). Compound **19** was prepared using the same method as described for **18** (Method F) starting from **9a** (39.29 mg, 0.101 mmol), 3-fluorophenol (17 mg, 0.152 mmol), and 1N NaOH (aq) (116µL, 0.116 mmol) in 2 mL of CH_2Cl_2 and 1 mL of H_2O. The reaction was shaken at rt overnight and was then worked up in the usual

manner to yield 11 mg (23.4 %) of **19**: HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{24}H_{20}FN_3O_6$, 466.14089; found, 466.14055; the purity of **27** was evaluated by two HPLC systems and found to be 100 % (system C, retention time = 5.75 min) and 100 % (system D, retention time = 14.06 min).

2-[3-(Ethylamino)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (20). Compound **20** was prepared using the same method as described for **18** (Method F) starting from **9a** (39.29 mg, 0.101 mmol), 3-ethylaminophenol (20.82 mg, 0.152 mmol), and 1N NaOH (aq) (116µL, 0.116 mmol) in 2 mL of CH_2Cl_2 and 1 mL of H_2O. The reaction was shaken at rt overnight and was then worked up in the usual manner to yield 4.0 mg (8 %) of **20**: HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{26}H_{26}N_4O_6$, 491.19251; found, 491.19296; The purity of **20** was evaluated by two HPLC systems and found to be 92 % (system C, retention time = 4.22 min) and 90 % (system D, retention time = 11.64 min).

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylaziridin-1-yl)benzo-1,4-quinone (21). Compound **21** was prepared using the same method as described for **10** (Method A) In this instance, a mixture of **9a** (100 mg, 0.26 mmol) and propylene imine (59 mg, 1.04 mmol) was added to pyridine hydrochloride (59 mg, 0.51 mmol) in dry THF (2 mL). The reaction was sonicated at 40 ^oC for 3 h. The reaction mixture was filtered. The residue was dissolved in CH_2Cl_2 and filtered through magnesol. The solvent was removed in vacuo. The resulting solid was recrystallized from CH_3CN-CH_2Cl_2 to yield 97 mg (90%) of **21**: MS (ESI) *m*/*z* 411.2; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{21}H_{22}N_4O_5$, 411.16630; found, 411.16554; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 5.54 Hz, 3 H), 2.19 (d, *J* = 3.78 Hz, 1 H), 2.25 (d, *J* = 5.79 Hz, 1 H), 2.40-2.53 (m, 1 H), 3.48 (s, 3 H), 3.84-3.96 (m, 2 H), 4.07 (s, 3 H), 4.25-4.40 (m, 2 H), 6.05 (s, 1 H), 7.08 (s, 1 H), 7.31 (s, 1 H), 7.96 (s, 1 H), 8.82 (d, J = 8 Hz, 2 H); Anal. ($C_{21}H_{22}N_4O_5$) C, H, N.

2-(4-Benzylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (22). This compound **22** was prepared using the same method as described for **10** (Method A) starting from 75 mg (0.19 mmol) of **9a**, 22 mg (0.19mmol) of pyridine hydrochloride, and 133 mg (0.76 mmol) of 4-benzylpiperidine in 1.5 mL dry THF. The reaction was sonicated at 40 ^oC for 3 h. The product was recrystallized from CH_3CN-CH_2Cl_2 to yield 47 mg (47%) of **22**: MS (ESI) *m*/*z* 529.2; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{30}H_{32}N_4O_5$, 529.24455; found, 529.24414; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37-1.51 (m, 2 H), 1.76-1.84 (m, *J* = 14.10 Hz, 2 H), 1.84-1.95 (m, 1 H), 2.59 (d, *J* = 7.05 Hz, 2 H), 2.89-3.09 (m, 1 H), 3.41-3.56 (m, 3 H), 3.84-3.93 (m, 2 H), 4.04-4.11 (m, 3 H), 4.19-4.29 (m, 1 H), 4.30-4.40 (m, 2 H), 5.76 (s, 1 H), 7.11 (s, 1 H), 7.13-7.18 (m, *J* = 7.05 Hz, 2 H), 7.22 (t, *J* = 7.30 Hz, 1 H), 7.27-7.34 (m, 2 H), 7.76-7.84 (m, 1 H), 8.82 (s, 1 H), 9.06 (s, 1 H); Anal. ($C_{30}H_{32}N_4O_5$.0.66 H_2O) C, H, N.

2-(4-Benzylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (23). This compound was prepared using the same method as described for **10** (Method A) starting from 100 mg (0.257 mmol) of **9a**, 89 mg

(0.77mmol) of pyridine hydrochloride and 446 mg (2.5 mmol) of benzylpiperazine in 1.0 mL dioxane. The materials were stirred in microwave reaction at 75 ^{o}C for 5 min. The reaction mixture was directly purified on Gilson reverse phase HPLC (column size: 150 x 30 mm, solvent system: 20%-80% CH_3CN-CH_3OH) to yield 136.1 mg (62%) of **23**: MS (ESI) *m*/*z* 530.2 $(M+H)^{+1}$, 265.6 $(M+2H)^{+2}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{29}H_{31}N_5O_5$, 530.23980; found, 530.24033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 4 H), 3.41-3.53 (s, 3 H), 3.66-3.84 (m, 6 H), 3.85-3.92 (m, 2 H), 4.01-4.09 (s, 3 H), 4.30-4.38 (m, 2 H), 5.76 (s, 1 H), 7.09 (s, 1 H), 7.32-7.43 (m, 6 H), 7.82 (s, 1 H), 8.81 (s, 1 H), 8.96 (s, 1 H). The purity of **23** was evaluated by two HPLC systems and found to be 95 % (system A, retention time = 3.17 min) and 99 % (system B, retention time = 8.6 min).

2-(4-Ethylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (24). Compound **24** was prepared using the same method as described for **10** (Method A) starting from 100 mg (0.257 mmol) of **9a**, 89 mg (0.77mmol) of pyridine hydrochloride, and 345 mL (2.57 mmol) of 1-ethylpiperazine in 1.0 mL dioxane. The materials were stirred in microwave reaction at 75 ^{o}C for 5 min. The reaction mixture was directly purified on Gilson reverse phase HPLC (column size: 150 x 30 mm, solvent system: 20%-80% CH_3CN/ CH_3OH). The product fraction was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated to yield 120 mg (64%) of **24**: MS (ESI) *m*/*z* 468.2 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{24}H_{29}N_5O_5$, 468.22415; found, 468.22404. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 6.55 Hz, 3 H), 2.93-3.08 (m, 6 H), 3.49 (s, 3 H), 3.83-3.92 (m, 2 H), 3.95 (m, 4 H), 4.07 (s, 3 H), 4.26-4.39 (m, 2 H), 5.82 (s, 1 H), 7.07 (s, 1 H), 7.31 (s, 1 H), 7.86 (s, 1 H), 8.82 (s, 1 H), 8.89 (s, 1 H). The purity of **24** was evaluated by two HPLC systems and found to be 97 % (system A, retention time = 2.09 min) and 95 % (system B, retention time = 6.26 min).

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-pyrrolidin-1-ylbenzo-1,4-quinone (25). Compound **25** was prepared using the same method as described for **10** (Method A) starting from 525 mg (1.35 mmol) of **9a**, 155 mg (1.35 mmol) of pyridine hydrochloride, and 0.56 mL (6.75 mmol) of pyrrolidine in 1.5 mL dry THF. The reaction was sonicated at 40 ^{o}C for 3 h. The product was recrystallized from CH_3CN and CH_2Cl_2 to yield 417 mg (72 %) of **25**: MS (ESI) *m*/*z* 425.2 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{22}H_{24}N_4O_5$, 425.18195; found (ESI_FTMS, $(M+H)^{1+}$), 425.1802; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97-2.07 (m, 4 H), 3.42 (m, 2 H), 3.49 (s, 3 H), 3.81-3.92 (m, 2 H), 4.01 (m, 2 H), 4.04-4.11 (s, 3 H), 4.25-4.42 (m, 2 H), 5.56 (s, 1 H), 7.06-7.19 (s, 1 H), 7.32-7.33 (s, 1 H), 7.81 (s, 1 H), 8.78-8.86 (s, 1 H), 9.29 (s, 1 H); Anal. ($C_{22}H_{24}N_4O_5$.0.66 H_2O) C, N, H: calcd, 5.41; found, 5.85.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pyridin-3-ylmethoxy) benzo-1,4-quinone (27). Compound **27** was prepared using the same method as described for **26** (Method E) starting from **9a** (60 mg, 0.15 mmol), 3-(hydroxymethyl)pyridine (167.86 mg, 1.54 mmol), and NaOPh-3H_2O (51 mg, 0.3 mmol) in 2 mL of CH_2Cl_2. The reaction was shaken at rt overnight. Then it was worked up in the usual manner to yield 12.0 mg (17.3 %) of **27**: MS (ESI) *m*/*z* 463.2 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{24}H_{22}N_4O_6$, 463.16121; found, 463.1608; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.89 (m, 2 H), 4.07 (s, 3 H), 4.34 (m, 2H), 5.13 (s, 2

H), 6.08 (s, 1 H), 7.05 (s, 1 H), 7.32 (s, 1 H), 7.38 (dd, *J* = 7.55, 4.53 Hz, 1 H), 7.81-7.86 (m, 1 H), 8.09 (s, 1 H), 8.66 (dd, *J* = 4.78, 1.51 Hz, 1 H), 8.68-8.72 (m, 2 H), 8.82 (s, 1 H); Anal. ($C_{24}H_{22}N_4O_6$) C, H, N.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-phenoxyethoxy)benzo-1,4-quinone (28). Compound **28** was prepared using the same method as described for **26** (Method E) starting from **9a** (60 mg, 0.15 mmol), 2-phenoxyethanol (213 mg, 1.54 mmol), and NaOPh-3H_2O (51 mg, 0.3 mmol) in 2 mL of CH_2Cl_2 yielding 9.0 mg (12 %) of **28**: HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{26}H_{25}N_3O_7$, 492.17653; found, 492.17554. The purity of **28** was evaluated by two HPLC systems and found to be 95 % (system F, retention time = 12.87 min) and 92 % (system B, retention time = 15.57 min).

2-Isopropoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (29). Compound **29** was prepared using the same method as described for **26** (Method E) starting from **9a** (208 mg, 0.53 mmol), isopropanol (0.41 ml, 5.34 mmol), and NaOPh-3H_2O (181.9 mg, 1.07 mmol) in 500 mL of CH_2Cl_2. The reaction was stirred at 25 ^oC for 2 h. It was diluted with H_2O and extracted with EtOAc, The EtOAc layer was dried over Na_2SO_4 and concentrated. The residue was purified by a Gilson HPLC. The combined fractions was extracted from saturated $NaHCO_3$ and washed with brine. The solution was dried over Na2SO_4 and the solvent was evaporated in vacuo to yield 92.5 mg (42 %) of **29** as an orange solid: MS (ESI) *m*/*z* 414.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{21}H_{23}N_3O_6$, 414.16596; found, 414.16758; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.04 Hz, 6 H), 3.49 (s, 3 H), 3.89 (m, 2 H), 4.07 (s, 3 H), 4.34 (m, 2 H), 4.49-4.64 (m, 1 H), 5.95 (s, 1 H), 7.07 (s, 1 H), 8.04 (s, 1 H), 8.77 (s, 1 H), 8.82 (s, 1 H). The purity of **29** was evaluated by two HPLC systems and found to be 98 % (system A, retention time = 6.09 min) and 98 % (system B, retention time = 12.79 min).

3-Chloro-2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (30). Compound **30** was prepared using the same method as described for **26** (Method E) starting from **9b** (479.0 mg, 1.13 mmol), difluoropropanol, (4.65 g, 25.81 mmol), NaOPh-3(H_2O), (211 mg, 1.24 mmol), and K_2CO_3 (300.0 mg, 2.17 mmol). The reaction mixture was stirred at reflux temperature for 4 h and at rt overnight yielding, after work up 0.31 mg (56.7%) of **30** as a red crystalline solid: MS (ESI) *m*/*z* 484 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{21}H_{20}ClF_2N_3O_6$, 484.10815; found, 484.10815; ^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.86-3.92 (m, 2 H), 4.06 (s, 3 H), 4.26-4.41 (m, 2 H), 4.67-4.77 (m, 2 H), 4.82-4.88 (m, 2 H), 5.40-5.61 (m, 1 H), 7.04 (s, 1 H), 7.33 (s, 1 H), 8.00-8.05 (s, 1 H), 8.70 (s, 1 H), 8.79-8.88 (s, 1 H). The purity of **30** was evaluated by two HPLC systems and found to be 100 % (system A, retention time = 8.42 min) and 92 % (system B, retention time = 14.94 min).

3-Chloro-2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (31). Compound **31** was prepared using the same method as described for **26** (Method E) starting from **9b** (479

mg, 1.13 mmol), 3-fluorobenzyl alcohol (1.42 g, 11.29 mmol), and NaOPh-$3H_2O$ (211mg, 1.24 mmol) in 60 mL of CH_2Cl_2. The reaction was stirred at 25 ^oC for 27 h. It was poured into dilute K_2CO_3 and extracted with $CHCl_3$ yielding 330 mg (56.8 %) of **31**: MS (ESI) *m/z* 514 $(M+H)^{+1}$; ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3 H), 3.84-3.93 (m, 2 H), 4.03-4.07 (s, 3 H), 4.29-4.38 (m, 2 H), 5.72 (s, 2 H), 6.99-7.09 (m, 2 H), 7.17-7.24 (m, 2 H), 7.31-7.34 (m, 2 H), 7.97-8.03 (s, 1 H), 8.72 (s, 1 H), 8.83 (s, 1 H); Anal. ($C_{25}H_{21}ClFN_3O_6$) C, H, N.

3-Chloro-2-ethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (32). Compound **32** was prepared using the same method as described for **26** (Method E) starting from **9b** (700 mg, 1.65 mmol), ethanol (30 ml, 517.2 mmol), NaOPh-$3H_2O$ (294.8 mg, 1.73 mmol), and K_2CO_3 (500 mg, 3.6 mmol) in 80 mL of CH_2Cl_2. The reaction was stirred at 25 ^oC for 7 h. and 8 drops of HOAc was added. The usual work-up yielded 350 mg (48.9 %) of **32**: MS (ESI) m/z 434.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{20}H_{20}ClN_3O_6$, 434.11134; found, 434.11093; ^1H NMR (400 MHz, *$CDCl_3$*) δ 1.46 (t, J = 7.05 Hz, 3 H), 3.49 (s, 3 H), 3.81-3.96 (m, 2 H), 4.06 (s, 3 H), 4.26-4.38 (m, 2 H), 4.75 (q, J = 7.05 Hz, 2 H), 7.05 (s, 1 H), 7.32 (s, 1 H), 7.98 (s, 1 H), 8.76-8.77 (s, 1 H), 8.83 (s, 1 H). The purity of **32** was evaluated by two HPLC systems and found to be 95 % (system A, retention time = 8.79 min) and 94 % (system D, retention time = 15.43 min).

2-[(2-Fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (33). Compound **33** was prepared using the same method as described for **26** (Method E) starting from **9a** (200 mg, 0.514 mmol), 2-fluorobenzyl alcohol (1.65 mL, 15.42 mmol), and NaOPh-$3H_2O$ (192.4 mg, 1.13 mmol) in 4 mL of CH_2Cl_2. The product was purified on a Gilson HPLC to yield 176.7 mg (72 %) of **33**: MS (ESI) *m/z* 480.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{25}H_{22}FN_3O_6$, 480.15654; found, 480.1564; ^1H NMR (400 MHz, $CDCl_3$) δ 3.45-3.48 (m, 3 H), 3.82-3.94 (m, 2 H), 4.05-4.10 (m, 3 H), 4.32-4.44 (m, 2 H), 5.18 (s, 2 H), 6.12 (s, 1 H), 7.08 (s, 1 H), 7.09-7.17 (m, 1 H), 7.17-7.24 (m, 1 H), 7.32-7.43 (m, 1 H), 7.48-7.56 (m, 2 H), 8.04 (s, 1 H), 8.86 (s, 1 H), 8.87 (s, 1 H). The purity of **33** was evaluated by two HPLC systems and found to be 90 % (system A, retention time = 8.6 min) and 91 % (system B, retention time = 15.4 min).

2-[(3-Fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino} benzo-1,4-quinone (34). Compound **34** was prepared using the same method as described for **26** (Method E) starting from **9a** (200 mg, 0.514 mmol), 3-fluorobenzyl alcohol (1.67 mL, 15.42 mmol), and NaOPh-$3H_2O$ (192.4 mg, 1.13 mmol) in 4 mL of CH_2Cl_2 yielding 144.1 mg (58 %) of **34**: MS (ESI) *m/z* 480.2 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{25}H_{22}FN_3O_6$, 480.15654; found, 480.15514; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43-3.53 (m, 3 H), 3.83-3.93 (m, 2 H), 4.07 (s, 3 H), 4.28-4.39 (m, 2 H), 5.11 (s, 2 H), 6.02 (s, 1 H), 7.02-7.12 (m, 2 H), 7.16 (d, *J* = 9.06 Hz, 1 H), 7.19-7.24 (m, 1 H), 7.32-7.44 (m, 2 H), 8.08 (s, 1 H), 8.73 (s, 1 H), 8.82 (s, 1 H). The purity of **34** was evaluated by two HPLC systems and found to be 99 % (system A, retention time = 8.8 min) and 99 % (system B, retention time = 15.7 min)

2-[(4-Fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino} benzo-1,4-quinone (35). Compound **35** was prepared using the same method as described for **26** (Method E) starting from **9a** (200 mg, 0.514 mmol), 4-fluorobenzyl alcohol (1.68 ml, 15.42 mmol) and NaOPh-3H_2O (192.4 mg, 1.13 mmol) in 4 mL of CH_2Cl_2 yielding 132.8 mg (54 %) of **35**: MS (ESI) *m*/*z* 480.2 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{25}H_{22}FN_3O_6$, 480.15654; found, 480.15548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3 H), 3.83-3.93 (m, *J* = 5.41, 3.90 Hz, 2 H), 4.06 (s, 3 H), 4.27-4.39 (m, 2 H), 5.07 (s, 2 H), 6.03 (s, 1 H), 7.04 (s, 1 H), 7.06-7.15 (m, 2 H), 7.31 (s, 1 H), 7.37-7.48 (m, 2 H), 8.06 (s, 1 H), 8.70 (s, 1 H), 8.81 (s, 1 H). The purity of **35** was evaluated by two HPLC systems and found to be 98 % (system A, retention time = 8.7 min) and 97 % (system B, retention time = 15.4 min).

2-Ethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (36). Compound **36** was prepared using the same method as described for **26** (Method E) starting from **9a** (389 mg, 1.0 mmol), ethanol (0.87 ml, 15 mmol), and NaOPh-3H_2O (255 mg, 1.5 mmol) in 10 mL of CH_2Cl_2. The reaction was stirred at 25 ^{o}C overnight. It was worked up in the usual manner and purified using preparative TLC plate, eluting with 3 % isopropanol-CH_2Cl_2 to yield 228 mg (57 %) of **36** as a red solid: MS (ESI) *m*/*z* 400.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{20}H_{21}N_3O_6$, 400.15031; found, 400.15058; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (t, *J* = 6.92 Hz, 3 H), 3.49 (s, 3 H), 3.86-3.94 (m, 2 H), 4.07 (s, 3 H), 4.11 (q, *J* = 7.05 Hz, 2 H), 4.34 (m, 2 H), 5.96 (s, 1 H), 7.06 (s, 1 H), 7.32 (s, 1 H), 8.06 (s, 1 H), 8.75 (s, 1 H), 8.81 (s, 1 H). The purity of **36** was evaluated by two HPLC systems and found to be 100 % (system A, retention time = 4.96 min) and 98 % (system B, retention time = 11.84 min).

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2,2,2-trifluoro-1-phenylethoxy)benzo-1,4-quinone (37). Compound **37** was prepared using the same method as described for **26** (Method E) starting from **9a** (200 mg, 0.514 mmol), α-(trifluoromethyl)benzyl alcohol (904 mg, 5.14 mmol), NaOPh-3H_2O (207.2 mg, 1.22 mmol), and K_2CO_3 (112.3 mg, 0.81 mmol) in 5 mL of CH_2Cl_2. The reaction was stirred at 25 ^{o}C overnight and worked up in the usual manner to yield 179.8 mg (66 %) of **37** as a red solid: MS (ESI) *m*/*z* 530.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{26}H_{22}F_3N_3O_6$, 530.15335; found, 530.15321; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41-3.52 (m, 3 H), 3.82-3.94 (m, 2 H), 4.04 (s, 3 H), 4.27-4.37 (m, 2 H), 5.45 (q, *J* = 5.96 Hz, 1 H), 5.84 (s, 1 H), 6.99 (s, 1 H), 7.31 (s, 1 H), 7.42-7.54 (m, 5 H), 8.07 (s, 1 H), 8.56 (s, 1 H), 8.82 (s, 1 H); Anal. ($C_{26}H_{22}F_3N_3O_6$) C, H, N.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(pentafluorobenzyl)oxy]benzo-1,4-quinone (38). Compound **38** was prepared using the same method as described for **26** (Method E) starting from **9a** (200 mg, 0.51 mmol), 2,3,4,5,6-pentafluorobenzyl alcohol (1.53g, 7.71 mmol), and NaOPh-3H_2O (132 mg, 0.77 mmol) in 9 mL of CH_2Cl_2 yielding 187.4 mg (60 %) of **38** as a red solid: MS (ESI) *m*/*z* 552.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{25}H_{18}F_5N_3O_6$, 552.11885; found, 552.1169; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.82-3.94 (m, 2 H), 4.08 (s, 3 H), 4.24-4.42 (m, 2 H), 5.13 (s, 2 H), 6.16 (s, 1 H), 7.07 (s, 1 H), 7.33 (s, 1 H), 8.10 (s, 1 H), 8.71 (s, 1 H), 8.82 (s, 1 H). The purity of 61 was evaluated by two HPLC

systems and found to be 100 % (system A, retention time = 9.9 min) and 97 % (system B, retention time = 16.58 min).

2-(2,2-Difluoroethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (39). Compound **39** was prepared using the same method as described for **26** (Method E) starting from **9a** (316.1 mg, 0.81 mmol), 2,2-difluoroethanol (1.0 g, 12.18 mmol), NaOPh-3H_2O (207.2 mg, 1.22 mmol), and K_2CO_3 (112.3 mg, 0.81 mmol) in 5 mL of CH_2Cl_2 to yield 66.6 mg (18 %) of **39** as a red solid: MS (ESI) *m/z* 436.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{20}H_{19}F_2N_3O_6$, 436.13147; found, 436.13104; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.86-3.92 (m, 2 H), 4.07 (s, 3 H), 4.22 (td, *J* = 12.40, 4.15 Hz, 2 H), 4.34 (m, 2 H), 6.02 (s, 1 H), 6.22 (tt, *J* = 54.61, 4.06 Hz, 1 H), 7.05 (s, 1 H), 7.33 (s, 1 H), 8.10 (s, 1 H), 8.68 (s, 1 H), 8.82 (s, 1 H); Anal. ($C_{20}H_{19}F_2N_3O_6$.0.33H_2O) C, H, N: calcd, 9.00; found, 9.52.

2-{[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone (40). Compound **40** was prepared using the same method as described for **26** (Method E) starting from **9a** (406.8 mg, 1.045 mmol), 3-phenyl-2-propyn-1-ol (2.07 g, 15.68 mmol), NaOPh-3H_2O (266 mg, 1.57 mmol), and K_2CO_3 (144.4 mg, 1.04 mmol) in 3 mL of CH_2Cl_2 yielding 79.8 mg (16 %) of **40** as a red solid: MS (ESI) *m/z* 486.1 $(M+H)^{+1}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{27}H_{23}N_3O_6$, 486.16596; found, 486.16532; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3 H), 3.89 (m, 2 H), 4.07 (s, 3 H), 4.34 (m, 2 H), 5.03 (s, 2 H), 6.26 (s, 1 H), 7.07 (s, 1 H), 7.29-7.40 (m, 4 H), 7.46 (dd, *J* = 7.93, 1.64 Hz, 2 H), 8.10 (s, 1 H), 8.74 (s, 1 H), 8.82 (s, 1 H). The purity of **40** was evaluated by two HPLC systems and found to be 100 % (system A, retention time = 9.5 min) and 99 % (system B, retention time = 16.57 min).

***N*-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-amine (58b)**. This compound was prepared from **56** (7.74 mg, 16 mmol), **57b** (6.2 g, 48 mmol), and sodium sodium bis(trimethylsilyl)amide (1.0 M in THF, 40 ml, 40 mmol) using the procedure described above for **58a**. The product was purified on a flash column of silica gel (2.8 x 25 cm), eluting with 25:25:1 CH_2Cl_2-EtOAc-CH_3OH, 5:1 EtOAc-CH_3OH and then 25:5:1 EtOAc-CH_3OH-Et_3N to yield 6.63 g (87 %) of **58b** as a white solid: MS (ESI) *m/z* 473.1 $(M+H)^{+1}$, 237 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, DMSO-D_6) δ 1.65-1.75 (m, 4 H), 1.89-2.00 (m, 2 H), 2.41-2.50 (m, 4 H), 2.57 (t, *J* = 7.18 Hz, 2 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 3.93 (s, 3 H), 4.18 (t, *J* = 6.42 Hz, 2 H), 7.15 (s, 1 H), 7.22 (s, 1 H), 7.38(s, 1 H), 7.78 (s, 1 H), 8.32 (s, 1 H), 9.17 (s, 1 H).

2-Chloro-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone (59a). This compound was prepared from **58a** (7.5 g, 15.86 mmol) and CAN (26.08 g, 47.57 mmol) in 200 mL of CH_3CN and 30 mL of H_2O using the procedure described above for **9e**. In this instance, the reaction was worked up in the usual manner and filtered through a pad of magnesol, eluted with 3:1 $CHCl_3$-isopropanol to give 0.74 g (10%) of **59a** as a red solid: MS (ESI) *m/z* 443.1 $(M+H)^{+1}$, 222.1 $(M+2H)^{+2}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{22}H_{23}ClN_4O_4$, 443.14806; found, 443.14908; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90-2.10 (m, 5 H), 2.12-2.28 (m, 2 H), 2.38-2.49 (s, 3 H), 3.09 (s, 2 H), 4.01-4.12 (m, 5 H), 7.03 (s, 1 H), 7.10 (s, 1 H), 7.29 (s, 1

H), 8.29 (s, 1 H), 8.49 (s, 1 H), 8.82-8.84 (m, 1 H); Anal. ($C_{22}H_{23}ClN_4O_4$.0.1 H_2O) C, H, N.

2-Chloro-5-[{6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl}amino]benzo-1,4-quinone (59b). This compound was prepared from **58b** (0.47 g, 1.0 mmol) and CAN (1.21 g, 2.2 mmol) in CH_3CN (10 mL) and H_2O (4 ml) using the procedure described above for **9e** to give 403 mg (91 %) of **59b** as a red solid. This compound was used without further purification.

2-Methoxy-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone (60). Compound **60** was prepared using the same method as described for **14** (Method C) starting from 133.0 mg (0.3 mmol) of **59a**, 3.0 mL (74.16 mmol) of methanol, and 84 µL (0.6 mmol) of triethylamine to yield 83 mg (63%) of **60** as a red solid: mp 165-175 °C; MS (ESI) *m/z* 439.2 $(M+H)^{+1}$, 240.6 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37-1.58 (m, 2 H), 1.63-1.81 (m, 1 H), 1.85-2.06 (m, 4 H), 2.30 (s, 3 H), 2.92 (d, *J* = 11.58 Hz, 2 H), 3.88-3.96 (s, 3 H), 4.04 (d, *J* = 6.30 Hz, 2 H), 4.07 (s, 3 H), 5.99 (s, 1 H), 7.06 (s, 1 H), 7.28 (s, 1 H), 8.07 (s, 1 H), 8.75 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{23}H_{26}N_4O_5$· 0.67 H_2O) C, H, N.

2-[2-Fluoro-1-(fluoromethyl)ethoxy]-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone (61). Compound **61** was prepared using the same method as described for **14** (Method C) starting from 164.0 mg (0.37 mmol) of **59a**, 0.36 g (3.7 mmol) of 1,3-difluoro-2-propanol, and 103 µL (0.74 mmol) of triethylamine to yield 132 mg (71%) of **61** as a red solid: mp 180-190 °C; MS (ESI) *m/z* 503.2 $(M+H)^{+1}$, 272.6 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.58 (m, 2 H), 1.66-1.80 (m, 1 H), 1.88-2.06 (m, 4 H), 2.31 (s, 3 H), 2.93 (d, *J* = 11.33 Hz, 2 H), 3.97-4.08 (m, 5 H), 4.64-4.70 (m, 2 H), 4.79-4.87 (m, 3 H), 6.13 (s, 1 H), 7.05 (s, 1 H), 7.28 (s, 1 H), 8.09 (s, 1 H), 8.68 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{25}H_{28}F_2N_4O_5$· 0.25 H_2CO_3) C, H, N.

2-Chloro-3-(cyclopropylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy) quinazolin-4-yl]amino}benzo-1,4-quinone (51). This compound was prepared from **9e** (650 mg, 1.55 mmol), $CsCO_3$ (1.01 g, 3.1 mmol), and cyclopropylmethanol (3.35 g, 46.45 mmol) as described above for **50**. The product was purified by thin layer chromatography, eluting with EtOAc. The major red band was collected and the silica gel was extracted with EtOAc-isopropanol. The solvent was removed to yield 0.143 g (20.1%) of **51** as a red solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37-0.39 (m, 2 H) 0.63-0.69 (m, 2 H), 1.27-1.34 (m, 1 H), 3.49 (s, 3 H), 3.87-3.91 (m, 2 H), 4.07 (s, 3 H), 4.24 (d, *J* = 7.30 Hz, 2 H), 4.31-4.36 (m, 2 H), 7.03 (s, 1 H), 7.33 (s, 1 H), 8.21 (s, 1 H), 8.48 (s, 1 H), 8.82 (s, 1 H); Anal. ($C_{22}H_{22}ClN_3O_6$) C, H, N. Other chromatography fractions indicated the presence of **48**, but this compound was not isolated in a pure state.

2-Chloro-3-isopropoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (52). This was prepared from **9e** (600 mg, 1.43 mmol), $CsCO_3$ (931. g, 2.86 mmol), and isopropanol (42 ml, 548.5 mmol) as described above for **50**. The product was purified by chromatography on silica gel, eluting with $CHCl_3$-

EtOAc 1:1 to yield 0.07 g (10.9%) of **52** as a red powder: MS (ESI) *m*/*z* 448 $(M+H)^{+1}$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, *J* = 6.30 Hz, 6 H), 3.46-3.51 (s, 3 H), 3.85-3.91 (m, 2 H), 4.06-4.10 (s, 3 H), 4.31-4.35 (m, 2 H), 4.88-5.03 (m, 1 H), 7.04 (s, 1 H), 7.31-7.34 (s, 1 H), 8.21 (s, 1 H), 8.50 (s, 1 H), 8.81-8.83 (s, 1 H); Anal. ($C_{21}H_{22}ClN_3O_6$) C, H, N.

2-(Benzyloxy)-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone (63). Compound **63** was prepared using the same method as described for **62** (Method G) starting from **59a** (101.4 mg, 0.23 mmol), of benzyl alcohol (236.8 mg, 2.29 mmol), and cesium carbonate (149 mg, 0.457 mmol) in 2 mL CH_2Cl_2. The reaction mixture was stirred at rt for 3 h. In this instance the reaction was directly pass through a plug of magnesol, eluting with EtOAc, 5% CH_3OH-EtOAc, 10% CH_3OH-EtOAc, and 20% CH_3OH-EtOAc. The filtrate was concentrated in vacuo to yield 26.1 mg (22 %) of **63**: MS (ESI) *m*/*z* 515.1 $(M+H)^{+1}$, 278.5 $(M+2H)^{+2}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{29}H_{30}N_4O_5$, 515.22890; found, 515.22821; ^1H NMR (400 MHz, $CDCl_3$) δ 1.87-2.08 (m, 7 H), 2.32 (s, 3 H), 2.94 (d, *J* = 11.33 Hz, 2 H), 4.02-4.09 (m, 5 H), 5.14 (s, 2 H), 5.92-6.12 (s, 1 H), 7.05-7.07 (s, 1 H), 7.28 (s, 1 H), 7.36-7.45 (m, 5 H), 8.08 (s, 1 H), 8.72 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{29}H_{30}N_4O_5 \cdot 3.0\ H_2O$) C, H, N.

2-Methoxy-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (64). Compound **64** was prepared using the same method as described for **14** (Method C) starting from 0.39 g (0.88 mmol) of **59b**, 8.8 mL (74.16 mmol) of methanol, and 84 µL (0.6 mmol) of triethylamine in 6.0 mL CH_2Cl_2. The reaction was stirred at 25 ^oC for 4.5 h. After the solvent was evaporated under 25 ^oC, the residue was worked up and purified in the usual manner to yield 78 mg (58%) of **64** as a red solid: mp 100-110 °C; MS (ESI) *m*/*z* 439.1; MS (ESI) *m*/*z* 220 $(M+2H)^{+2}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{23}H_{26}N_4O_5$, 439.19760; found, 439.1981; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76-1.86 (m, 4 H), 2.11-2.22 (m, 2 H), 2.56 (s, 4 H), 2.69 (t, *J* = 7.30 Hz, 2 H), 3.92 (s, 3 H), 4.06-4.09 (s, 3 H), 4.23-4.31 (m, 2 H), 5.99 (s, 1 H), 7.06 (s, 1 H), 7.31-7.34 (s, 1 H), 8.07 (s, 1 H), 8.75 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{23}H_{26}N_4O_5 \cdot 3.0\ H_2O$) C, N, H: calcd, 6.04; found, 6.55.

2-{[6-Methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(3-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone (66). Compound **66** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of **59b** in 500 mL $CHCl_3$ was treated with 1-phenyl-1-propy-3-ol (2.38 g, 17.97 mmol) and NaOPh-$3H_2O$ (426.27 mg, 2.7 mmol. The usual workup gave 0.337 g (34.7 %) of **66** as an orange solid: MS (ESI) *m*/*z* 539.1 $(M+H)^{+1}$, 270.1 $(M+2H)^{+2}$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76-1.84 (m, 4 H), 2.06-2.23 (m, 2 H), 2.55 (s, 4 H), 2.67 (t, *J* = 7.30 Hz, 2 H), 4.04-4.12 (s, 3 H), 4.27 (t, *J* = 6.67 Hz, 2 H), 5.04 (s, 2 H), 6.26 (s, 1 H), 7.06 (s, 1 H), 7.30-7.39 (m, 4 H), 7.43-7.49 (m, 2 H), 8.10 (s, 1 H), 8.73 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{31}H_{30}N_4O_5.0.33\ H_2O$) C, H, N.

2-{[6-Methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(pyridin-2-ylmethoxy)benzo-1,4-quinone (67). Compound **67** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with (17.97 mmol) of pyridine-2-

methanol and 426 mg (2.7 mmol) of NaOPh-3H_2O. The usual workup gave 0.16 g (17.2 %) of **67** as a red solid: MS (ESI) *m*/*z* 516.1 $(M+H)^{+1}$, 258.5 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 4 H), 2.08-2.22 (m, 2 H), 2.55 (s, 4 H), 2.68 (t, *J* = 7.30 Hz, 2 H), 4.04-4.11 (s, 3 H), 4.27 (t, *J* = 6.67 Hz, 2 H), 5.25 (s, 2 H), 6.12 (s, 1 H), 7.05 (s, 1 H), 7.29-7.35 (m, 2 H), 7.58 (d, *J* = 7.81 Hz, 1 H), 7.75-7.81 (m, 1 H), 8.09 (s, 1 H), 8.62 (d, *J* = 4.28 Hz, 1 H), 8.72 (s, 1 H), 8.82 (s, 1 H); Anal. ($C_{28}H_{29}N_5O_5$.0.75 H_2O) C, H, N.

2-(Benzyloxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (68). Compound **68** was prepared using the same method as described for **65** (Method E) starting with **58b** (870 mg, 1.84 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 1.99 g (18.39 mmol) of benzyl alcohol and 392.67 mg (2.48 mmol) of NaOPh-3H_2O. After stirring, the usual workup gave 0.3 g (31.7 %) of **68** as a red solid: MS (ESI) *m*/*z* 515.1 $(M+H)^{+1}$, 258 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74-1.88 (m, 4 H), 2.03-2.25 (m, 2 H), 2.55 (s, 4 H), 2.68 (t, *J* = 7.30 Hz, 2 H), 3.98-4.12 (s, 3 H), 4.27 (t, *J* = 6.67 Hz, 2 H), 5.14 (s, 2 H), 6.04 (s, 1 H), 6.99-7.12 (s, 1 H), 7.29-7.35 (s, 1 H), 7.35-7.48 (m, 5 H), 8.07 (s, 1 H), 8.72 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{29}H_{30}N_4O_5$· 0.5 H_2O) C, H, N.

2-{[6-Methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(penta fluorobenzyl)oxy]benzo-1,4-quinone (69). Compound **69** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 3.56 g (18.0 mmol) of 2,3,4,5,6-pentafluorobenzyl alcohol and 398 mg (2.34 mmol) of NaOPh-3H_2O. The usual workup gave 66 mg (6 %) of **69** as a red solid: MS (ESI) *m*/*z* 605.1 $(M+H)^{+1}$, 323.5 $(M+2H)^{+2}$; HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{29}H_{25}F_5N_4O_5$, 605.18179; found, 605.1804; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 4 H), 2.10-2.27 (m, 2 H), 2.67 (d, *J* = 48.60 Hz, 6 H), 4.09 (s, 3 H), 4.28 (t, *J* = 6.42 Hz, 2 H), 5.13 (s, 2 H), 6.16 (s, 1 H), 7.07 (s, 1 H), 7.33 (s, 1 H), 8.11 (s, 1 H), 8.72 (s, 1 H), 8.82 (s, 1 H); Anal. ($C_{29}H_{25}F_5N_4O_5$. 0.5 H_2O) C, H, N.

2-{[6-Methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(1-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone (70). Compound **70** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 2.38 g (17.97 mmol) of 1-phenyl-1-propyn-1-ol and 369.43 mg (2.34 mmol) of NaOPh-3H_2O. After stirring, the usual workup gave 308 mg (31.8 %) of **70** as a red solid: MS (ESI) *m*/*z* 539.1 $(M+H)^{+1}$, 270.1 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 4 H), 2.11-2.22 (m, 2 H), 2.56 (s, 4 H), 2.69 (s, 2 H), 2.89 (d, *J* = 2.27 Hz, 1 H), 4.08 (s, 3 H), 4.27 (t, *J* = 6.55 Hz, 2 H), 5.85 (d, *J* = 2.27 Hz, 1 H), 6.31 (s, 1 H), 7.06 (s, 1 H), 7.33 (s, 1 H), 7.41-7.49 (m, 3 H), 7.62 (dd, *J* = 7.43, 1.89 Hz, 2 H), 8.07 (s, 1 H), 8.70 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{31}H_{30}N_4O_5$. 1.0 H_2O) C, H, N.

2-{[6-Methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(prop-2-yn-1-yloxy)benzo-1,4-quinone (71). Compound **71** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 2.84 g (50.74 mmol) of propargyl

alcohol and 347.7 mg (2.2 mmol) of NaOPh-$3H_2O$. After stirring, the usual workup gave 288 mg (36.8 %) of **71** as an orange solid: MS (ESI) *m*/*z* 463.1 $(M+H)^{+1}$, 232 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.85 (m, 4 H), 2.11-2.22 (m, 2 H), 2.56 (s, 4 H), 2.64-2.78 (m, 3 H), 4.06-4.11 (s, 3 H), 4.28 (t, *J* = 6.67 Hz, 2 H), 4.81 (d, *J* = 2.52 Hz, 2 H), 6.17 (s, 1 H), 7.06 (s, 1 H), 7.33 (s, 1 H), 8.09 (s, 1 H), 8.71 (s, 1 H), 8.81 (s, 1 H). The purity of **71** was evaluated by two HPLC systems and found to be 100 % (system C, retention time = 1.98 min) and 98 % (system D, retention time = 8.01 min).

2-(Allyloxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (72). Compound **72** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 2.95 g (50.74 mmol) of allyl alcohol and 347.7 mg (2.2 mmol) of NaOPh-$3H_2O$. The usual workup gave 220 mg (28 %) of **72** as an orange solid: MS (ESI) *m*/*z* 465.1 $(M+H)^{+1}$, 233.1 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77-1.86 (m, 4 H), 2.10-2.22 (m, 2 H), 2.55 (s, 4 H), 2.68 (t, *J* = 7.30 Hz, 2 H), 4.07 (s, 3 H), 4.27 (t, *J* = 6.67 Hz, 2 H), 4.61 (d, *J* = 5.54 Hz, 2 H), 5.25-5.59 (m, 2 H), 5.98 (s, 1 H), 6.01-6.15 (m, 1 H), 7.06 (s, 1 H), 7.32 (s, 1 H), 8.07 (s, 1 H), 8.73 (s, 1 H), 8.81 (s, 1 H); Anal ($C_{25}H_{28}N_4O_5 \cdot 0.4\ H_2O$) C, H, N.

2-{[6-Methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(1-methylprop-2-yn-1-yl)oxy]benzo-1,4-quinone (73). Compound **73** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 3.9 g (55.8 mmol) of 1-butyn-3-ol and 401.2 mg (2.54 mmol) of NaOPh-$3H_2O$. The usual workup gave 235 mg (29.2 %) of **73** as a red solid: MS (ESI) *m*/*z* 477.2 $(M+H)^{+1}$, 239.1 $(M+2H)^{+2}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (d, *J* = 6.55 Hz, 7 H), 2.10-2.25 (m, 2 H), 2.56 (s, 4 H), 2.63-2.73 (m, 3 H), 4.08 (s, 3 H), 4.27 (t, *J* = 6.67 Hz, 2 H), 4.74-4.92 (m, 1 H), 6.21 (s, 1 H), 7.06 (s, 1 H), 7.33 (s, 1 H), 8.07 (s, 1 H), 8.72 (s, 1 H), 8.81 (s, 1 H); Anal. ($C_{26}H_{28}N_4O_5 \cdot 0.66H_2O$) C, H, N.

2-(2-Furylmethoxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino} benzo-1,4-quinone (74). Compound **74** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 1.77 g (18.0 mmol) of furfuryl alcohol and 398 mg (2.34 mmol) of NaOPh-$3H_2O$. The usual workup gave 90.0 mg (9.9 %) of **74** as a red solid: HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{27}H_{28}N_4O_6$, 505.20816; found, 505.2077; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 4 H), 2.09-2.22 (m, 2 H), 2.56 (s, 4 H), 2.69 (t, *J* = 7.05 Hz, 2 H), 4.03-4.11 (s, 3 H), 4.27 (t, *J* = 6.67 Hz, 2 H), 5.09 (s, 2 H), 6.19 (s, 1 H), 6.42 (dd, *J* = 3.27, 1.76 Hz, 1 H), 6.56 (d, *J* = 3.02 Hz, 1 H), 7.06 (s, 1 H), 7.33 (s, 1 H), 7.48 (d, *J* = 1.26 Hz, 1 H), 8.07 (s, 1 H), 8.73 (s, 1 H), 8.80 (s, 1 H); Anal. ($C_{27}H_{28}N_4O_6 \cdot 1.33H_2O$) C, H, N.

2-(2,2-Difluoroethoxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (75). Compound **75** was prepared using the same method as described for **65** (Method E) starting with **58b** (850 mg, 1.8 mmol). The solution of the **59b** in 500 mL $CHCl_3$ was treated with 1.47 g (18.0

mmol) of 2,2-difluoro ethanol and 398 mg (2.34 mmol) of NaOPh-3H_2O. The usual workup gave 42.6 mg (5 %) of **75** as a red solid: HRMS (ESI-FTMS $(M+H)^{+1}$): calcd for $C_{24}H_{26}F_2N_4O_5$, 489.19440; found, 489.1956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78-1.85 (m, 4 H), 2.13-2.22 (m, 2 H), 2.59 (s, 4 H), 2.71 (t, *J* = 7.30 Hz, 2 H), 4.08 (s, 3 H), 4.18 (d, *J* = 4.03 Hz, 1 H), 4.22 (d, *J* = 4.03 Hz, 1 H), 4.24-4.30 (m, 3 H), 6.02 (s, 1 H), 7.05 (s, 1 H), 7.33 (s, 1 H), 8.10 (s, 1 H), 8.68 (s, 1 H), 8.82 (s, 1 H); Anal. ($C_{24}H_{26}F_2N_4O_5 \cdot 0.5H_2O$) C, H, N.

Indications of compound purity

Elemental Analyses:

	Found			**Calcd.**				
Comp	**C**	**H**	**N**	**C**	**H**	**N**	**formula**	**hydration**
21	61.33	5.32	13.62	61.46	5.4	13.65	C21H22N4O5	
9c	53.79	4.14	9.92	53.59	4.42	9.87	C19H18ClN3O6	0.33
41	58.3	5.31	12.72	58.26	5.7	12.94	C21H24N4O6	0.25
22	66.93	5.92	10.44	66.65	6.21	10.36	C30H32N4O5	0.66
26	55.65	4.38	9.19	55.38	4.8	9.23	C21H21F2N3O6	0.33
9g	58.51	4.94	11.79	58.85	5.03	11.44	C18H17N3O5	0.66
9f	58.07	5.01	10.89	58.64	5.49	10.80	C19H19N3O5	1.1
9h	58.59	4.72	10.43	58.31	5.06	10.74	C19H19N3O6	0.33
42	58.13	4.64	12.04	58.13	4.88	12.33	C22H22N4O7	
37	58.73	4.3	7.89	58.98	4.19	7.94	C26H22F3N3O6	
9m	49.96	3.47	9.54	49.79	3.71	9.68	C18H16BrN3O5	
64	56.09	6.04	11.36	56.09	6.55	11.38	C23H26N4O5	3.0
63	61.2	6.05	9.53	61.26	6.38	9.85	C29H30N4O5	3.0
25	60.18	5.41	12.6	60.54	5.85	12.84	C22H24N4O5	0.66
9k	49.30	3.35	9.46	49.28	3.79	9.58	C18H16BrN3O5	0.25
9j	57.89	4.42	11.15	58.29	4.48	11.33	C24H22N4O6S	
72	63.94	6.14	11.91	63.65	6.15	11.88	C25H28N4O5	0.4
75	57.51	5.05	11.07	57.94	5.47	11.26	C24H26F2N4O5	0.5
60	61.58	6.19	12.19	61.31	6.12	12.43	C23H26N4O5	0.67
39	54.46	4.18	9.00	54.42	4.49	9.52	C20H19F2N3O6	0.33
16	58.88	4.76	10.52	59.22	4.97	10.90	C19H19N3O6	
18	60.59	4.66	12.98	60.50	4.80	13.07	C27H23N5O6	1.25
27	62.03	4.45	12.27	62.33	4.80	12.11	C24H22N4O6	
9a	55.11	4.11	10.81	55.46	4.14	10.78	C18H16ClN3O5	

10	59.89	5.79	13.79	60.29	5.57	14.06	C20H22N4O5	
13	63.30	4.64	8.82	63.15	4.86	9.21	C24H21N3O6	0.5
17	62.61	5.87	12.59	63.00	5.98	12.78	C23H26N4O5	
14	57.36	5.18	9.48	57.53	5.52	9.58	C21H23N3O7	0.5
15	64.30	5.05	8.95	64.44	5.08	9.02	C25H23N3O6	0.25
21	60.43	5.29	13.30	60.13	5.53	13.36	C21H22N4O5	
9i	54.18	4.14	9.77	54.36	4.32	10.01	C19H18ClN3O6	
9e	53.29	4.32	10.05	53.22	4.47	9.80	C19H18ClN3O6	0.5
49	56.50	4.84	9.79	56.60	5.22	9.90	C20H21N3O7	0.5
52	55.96	4.73	9.14	56.32	4.95	9.38	C21H22ClN3O6	
51	57.72	4.78	8.94	57.46	4.82	9.14	C22H22ClN3O6	
61	58.37	5.18	10.50	58.55	5.55	10.82	C25H28F2N4O5	0.25
66	68.64	5.68	10.03	68.37	5.68	10.29	C31H30N4O5	0.33
67	63.72	5.80	13.08	63.56	5.81	13.24	C28H29N5O5	0.75
31	58.23	3.87	8.01	58.43	4.12	8.18	C25H21ClFN3O6	
68	66.24	5.99	10.62	66.52	5.97	10.70	C29H30N4O5	0.5
69	56.62	4.15	9.06	56.77	4.27	9.13	C29H25F5N4O5	0.5
70	66.92	5.52	10.12	66.89	5.79	10.07	C31H30N4O5	1.0
73	63.95	5.72	11.41	63.92	6.05	11.47	C26H28N4O5	0.66
74	61.41	5.61	10.67	61.35	5.85	10.60	C27H28N4O6	1.33

HPLC Purity

Comp	**Method 1**	**Purity 1**	**Retention Time**
65	MeCN/H2O 40 to 90, 254 nm	86%	2.03
50	MeCN/H2O 40 to 90, 254 nm	100%	3.89
12	MeCN/H2O 40 to 90, 254 nm	100%	5.49
9d	MeCN/H2O 40 to 90, 254 nm	100%	2.74
19	MeCN/H2O 40 to 90, 254 nm	100%	5.75
20	MeCN/H2O 40 to 90, 254 nm	92%	4.22
32	MeCN/H2O 30 to 90, 230 nm	95%	8.79
51	MeCN/H2O 30 to 90, 230 nm	93%	2.1
43	MeCN/H2O 10 to 90, 254 nm	95%	12.87
11	MeCN/H2O 40 to 90, 254 nm	93%	2.94
40	MeCN/H2O 40 to 90, 230 nm	94%	5.46
57	MeCN/H2O 30 to 90, 230 nm	100%	4.96
67	MeCN/H2O 30 to 90, 230 nm	100%	9.5
9l	MeCN/H2O 30 to 90, 230 nm	96.3%	6.16
38	MeCN/H2O 30 to 90, 230 nm	100%	9.9
29	MeCN/H2O 30 to 90, 230 nm	98%	6.09

33	MeCN/H2O 30 to 90, 230 nm	90%	8.6
34	MeCN/H2O 30 to 90, 230 nm	99%	8.8
35	MeCN/H2O 30 to 90, 230 nm	98%	8.7
9b	MeCN/H2O 30 to 90, 230 nm	99%	8.04
23	MeCN/H2O 30 to 90, 230 nm	95%	3.17
24	MeCN/H2O 30 to 90, 230 nm	97%	2.09
30	MeCN/H2O 30 to 90, 230 nm	100%	8.42
62	MeCN/H2O 20 to 60, 230 nm	98%	2.033

Comp	**Method 2**	**Purity 2**	**Retention Time**
65	MeOH/H2O 70 to 90, 254 nm	76%	7.79
50	MeOH/H2O 70 to 90, 254 nm	89%	12.2
12	MeOH/H2O 70 to 90, 254 nm	89.7%	15.40
9d	MeOH/H2O 70 to 90, 254 nm	96%	8.63
19	MeOH/H2O 70 to 90, 254 nm	100%	14.06
20	MeOH/H2O 70 to 90, 254 nm	90%	11.64
32	MeOH/H2O 70 to 90, 254 nm	94%	15.43
51	MeOH/H2O 70 to 90, 230 nm	91%	6.3
43	MeOH/H2O 70 to 90, 230 nm	92.2%	15.57
11	MeOH/H2O 70 to 90, 254 nm	100%	12.47
40	MeOH/H2O 70 to 90, 230 nm	92%	15.62
57	MeOH/H2O 70 to 90, 230 nm	98%	11.84
67	MeOH/H2O 70 to 90, 230 nm	99%	16.57
9l	MeOH/H2O 70 to 90, 230 nm	93%	12.78
38	MeOH/H2O 70 to 90, 230 nm	97%	16.58
29	MeOH/H2O 70 to 90, 230 nm	98%	12.79
33	MeOH/H2O 70 to 90, 230 nm	91%	15.4
34	MeOH/H2O 70 to 90, 230 nm	99%	15.7
35	MeOH/H2O 70 to 90, 230 nm	97%	15.4
9b	MeOH/H2O 70 to 90, 230 nm	98%	14.9
23	MeOH/H2O 70 to 90, 230 nm	99%	8.6
24	MeOH/H2O 70 to 90, 230 nm	95%	6.26
30	MeOH/H2O 70 to 90, 230 nm	92%	14.94
62	MeOH/H2O 70 to 90, 230 nm	98%	2.97

Analytical HPLC were conducted on an HP 1090 liquid chromatography system over a 4.6 mm x 150 mm YMC ODS-A column (5 um, 120A) using multiple wavelength uv detection (typically 230 and 254 nm).

System A: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (30-90% over 20 minutes)

- wavelength 230 nm
- flow rate of 1 mL/min

System B: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (70-90% over 20 minutes)
- wavelength 230 nm
- flow rate of 1 mL/min

System C: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (40-90% over 20 minutes)
- wavelength 254 nm
- flow rate of 1 mL/min

System D: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (70-90% over 20 minutes)
- wavelength 254 nm
- flow rate of 1 mL/min

System E: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (40-90% over 20 minutes)
- wavelength 230 nm
- flow rate of 1 mL/min

System F: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (10-90% over 20 minutes)
- wavelength 254 nm
- flow rate of 1 mL/min

System G: - a gradient elution of increasing concentrations of CH_3CN in water containing 0.02% TFA (20-60% over 20 minutes)
- wavelength 230 nm
- flow rate of 1 mL/min