Supporting Information

Selective Inhibition of EGFR and VEGFR2 Tyrosine Kinases Controlled by a Boronic Acid Substituent on 4-Anilinoquinazolines

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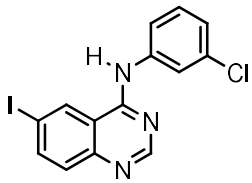
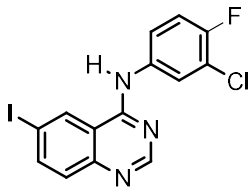
General Information. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL 300 (300 MHz) or VARIAN UNITY-INOVA 400 (400 MHz) spectrometers. The chemical shifts are reported in δ units relative to internal tetramethylsilane. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer. High-resolution mass spectra (ESI) were recorded on a Bruker Daltonics micro TOF-15 focus. Analytical thin layer chromatography (TLC) was performed on a glass plates of silica gel 60 GF_{254} (Merck). Column chromatography was conducted on silica gel (Merck Kieselgel 70-230 mesh). Most commercially supplied chemicals were used without further purification.

4-(3-Chloroanilino)-6-iodoquinazoline (3a)



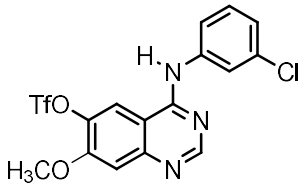
To a solution of 4-chloro-6-iodoquinazoline **1** (5.44 g, 18.8 mmol) in isopropanol (IPA; 150 mL) was added 3-chloroaniline (2.0 mL, 19 mmol). The mixture was stirred under reflux for 24 h and cooled to room temperature. The precipitate was filtered, washed with IPA and dried in vacuo to give **3a** (4.93 g, 12.9 mmol, 69% yield) as a white solid: ^{1}H NMR (400 MHz; CD_3OD) δ 8.99 (s, 1H), 8.77 (s, 1H), 8.32 (d, *J*=9.2Hz, 1H), 7.80 (s, 1H), 7.54－7.58 (m, 2H), 7.39 (t, *J*=8.0Hz, 1H), 7.29 (d, J=8.0Hz, 1H); ^{13}C NMR (75 MHz, DMSO-*d*6) δ 158.7, 151.6, 144.4, 139.1, 138.4, 133.2, 133.1, 130.1, 126.5, 124.3, 123.1, 122.3, 115.5, 94.5; IR (KBr) 3167, 3020, 1666, 1608, 1460, 918, 833, 563, 488 cm^{-1}; MS (APCI) m/z 382 ($[M+H]^+$), 423 ($[M+H+CH_3CN]^+$); Anal. Calcd for $C_{14}H_9ClIN_3$: C, 44.06; H, 2.38; N, 11.01; found: C, 43.09; H, 2.40; N, 10.99.

4-(3-Chloro-4-fluoroanilino)-6-iodoquinazoline (3b)



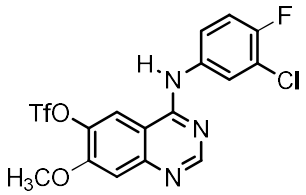
This compound was prepared from **1** (643 mg, 2.20 mmol) and 3-chloro-4-fluoroaniline (306 mg, 2.1 mmol) by the same procedure as described for compound **3a**.White solid (763 mg, 1.91 mmol, 87% yield): ^{1}H NMR (300 MHz; CD_3OD) δ 8.95 (d, *J*=3.0Hz, 1H), 8.74(s, 1H), 8.30 (dd, *J*=3.0Hz, 9.0Hz, 1H), 7.90 (dd, *J*=3.0Hz, 6.0Hz, 1H), 7.57－7.62 (m, 1H), 7.55 (d, *J*=9.0Hz, 1H), 7.28 (t, *J*=9.0Hz, 1H); ^{13}C NMR (75 MHz, DMSO-*d*6) δ 158.5, 156.9, 153.7, 151.6, 144.3, 139.5, 134.3, 134.2, 133.2, 126.4, 125.2, 125.1, 122.6, 119.5, 119.3, 117.2, 116.9, 115.5, 94.4; ; IR(KBr) 2984, 2596, 2361, 1609, 1560, 1499, 1437, 1367, 1263, 826, 777, 494 cm^{-1}; MS (APCI) m/z 400 ($[M+H]^+$), 441 ($[M+H+CH_3CN]$)$^+$); Anal. Calcd for $C_{14}H_8ClIFN_3$: C, 42.08; H, 2.02; N, 10.52; found: C, 42.49; H, 2.02; N, 10.45.

4-(3-Chloroanilino)-7-methoxyquinazolin-6-yl trifluoromethanesulfonate (5a)



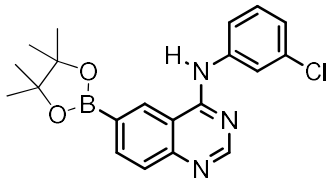
To a solution of **2** (504 mg, 1.99 mmol) in IPA (15 mL) was added 3-chloroaniline (0.23 ml, 2.19 mmol). The mixture was stirred under reflux for 2 h and cooled to room temperature. The precipitate was filtered, washed with IPA and dried in vacuo. The resulting solid was dissolved in methanol (10 mL) and aqueous ammonia (25%, 2 mL) was added. The mixture was stirred at room temperature for 8 h and the solvent was evaporated. The resulting solid was washed with dichloromethane and dried in vacuo. The solid was dissolved in pyridine (5 mL) and trifluoromethanesulfonic anhydride was added at 0 °C. The reaction temperature was allowed to warm to room temperature and the mixture was stirred for further 7 h. The solvent was evaporated and the residue was purified by silica gel column chromatography with hexane/ethyl acetate (4:1) to give **5a** (133 mg, 0.31 mmol, 15% yield in three steps) as a white solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.77 (s, 1H), 7.89 (s, 1H), 7.73 (s, 1H), 7.55 (d, J=8.4Hz, 1H), 7.42 (s, 1H), 7.36 (t, J=8.4Hz, 1H), 7.19 (d, *J*=9.2Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 156.1, 155.2, 151.1, 138.9, 138.1, 134.7, 130.0, 125.0, 122.3, 120.8, 120.2, 116.5, 115.0, 109.7, 108.5, 56.6; IR (KBr) 3620, 3450, 3119, 2359, 1630, 1533, 1421, 1219, 1119, 1001, 897, 770, 629, 502 cm^{-1}; MS (APCI) m/z 434 ($[M+H]^+$), 475($[M+H+CH_3CN]$)$^+$).

4-(3-Chloro-4-fluoroanilino)-7-methoxyquinazolin-6-yl trifluoromethanesulfonate (5b)



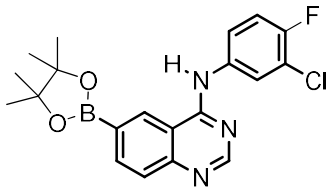
This compound was prepared from **2** (488 mg, 1.93 mmol) and 3-chloro-4-fluoroaniline (309 mg, 2.12 mmol) by the same procedure as described for compound **5a**.White solid (575 mg, 1.27 mmol, 66% yield): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.74 (s, 1H), 7.90 (dd, J=2.8Hz, 6.4Hz, 1H), 7.73 (s, 1H), 7.49－7.53 (m, 1H), 7.42 (s, 1H), 7.21 (t, J=8.8Hz, 1H), 4.07 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 157.0, 156.0, 155.3, 153.7, 150.8, 138.2, 134.2, 127.9, 124.9, 122.4, 122.3, 121.4, 121.2, 120.8, 116.9, 116.6, 115.0, 109.6, 108.3, 56.7; IR (KBr) 3452, 3411, 3126, 2359, 1630, 1504, 1421, 1219, 1132, 895 cm^{-1}; MS (ESI) m/z 452 ([M+H]$^+$).

4-(3-Chloroanilino)-6-pinacolatoborylquinazoline (6a)



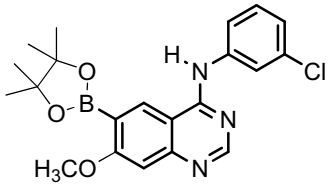
A mixture of **3a** (450 mg, 1.18 mmol), bispinacolatodiboron (331 mg, 1.30 mmol), $PdCl_2$ (21 mg, 0.12 mmol), 1,1'-bis(diphenylphosophino)ferrocene (66 mg, 0.12 mmol), and potassium acetate (347 mg, 3.54 mmol) in DMF (20 mL) was stirred at 80 °C under argon atmosphere for 2 h. After cooled to room temperature, the reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, and then concentrated. Purification by column chromatography on silica gel with hexane/ethyl acetate (4/1) as eluent to give **6a** (144 mg, 0.38 mmol, 32% yield) as a white solid: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.82 (s, 1H), 8.34 (s, 1H), 8.20 (dd, *J*=3.0Hz, 6.0Hz, 1H), 7.99 (t, *J*=3.0Hz, 1H), 7.90 (d, *J*=6.0Hz, 1H), 7.62－7.65 (m, 2H), 7.35 (t, *J*=6.0Hz, 1H), 7.16 (dd, *J*=3.0Hz, 6.0Hz, 1H), 1.41 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 155.6, 151.5, 139.3, 138.2, 134.5, 129.8, 128.2, 127.7, 124.4, 121.9, 119.8, 114.5, 84.4, 24.8; IR(KBr) 3059, 2980, 2322, 1622, 1526, 1435, 1352, 1143, 1097, 851 cm^{-1}; MS (APCI) m/z 382 ([M+H]$^+$), 423([M+H+CH_3CN])$^+$); Anal. Calcd for $C_{20}H_{21}BClN_3O_2$: C, 62.94; H, 5.55; N, 11.01; found: C, 61.60; H, 5.45; N, 10.91.

4-(3-Chloro-4-fluoroanilino)-6-pinacolatoborylquinazoline (6b)



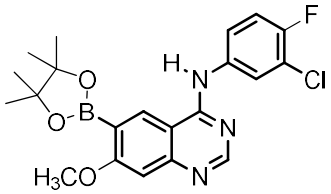
This compound was prepared from **3a** (411mg, 1.03 mmol), bispinacolatodiboron (289 mg, 1.14 mmol), $PdCl_2$ (18 mg, 0.10 mmol), 1,1'-bis(diphenylphosophino)ferrocene (55 mg, 0.10 mmol), and potassium acetate (303 mg, 3.15 mmol) by the same procedure as described for compound **6a**.White solid (174 mg, 0.44 mmol, 42% yield): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.80 (s, 1H), 8.33 (s, 1H), 8.20 (d, *J*=8.4Hz, 1H), 8.01 (dd, *J*=2.4Hz, 6.0Hz, 1H), 7.90 (d, *J*=8.4Hz, 1H), 7.56－7.61 (m, 2H), 7.20 (t, *J*=8.8Hz, 1H), 1.41 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.5, 155.5, 153.5, 153.3, 151.5, 138.2, 134.8, 128.2, 127.7, 124.4, 121.9, 121.8, 120.9, 116.6, 116.3, 114.4, 84.3, 24.8; IR(KBr) 3198, 2982, 2330, 1624, 1533, 1499, 1352, 1144, 1096, 851 cm^{-1}; MS(APCI) m/z 400 ($[M+H]^+$), 441($[M+H+CH_3CN]$)$^+$); Anal. Calcd for $C_{20}H_{20}BClFN_3O_2$: C, 60.11; H, 5.04; N, 10.51; found: C, 60.82; H, 5.06; N, 10.33.

4-(3-Chloroanilino)-7-methoxy-6-pinacolatoborylquinazoline (6c)



This compound was prepared from **5a** (40 mg, 0.09 mmol), bispinacolatodiboron (35 mg, 0.14 mmol), $PdCl_2$ (2 mg, 0.01 mmol), 1,1'-bis(diphenylphosophino)ferrocene (6 mg, 0.01 mmol), and potassium acetate (27 mg, 0.28 mmol) by the same procedure as described for compound **6a**. Further purification was carried out using gel permeation chromatography (GPC)-loaded recycle system with chloroform (LC-9201, Japan Analytical Industry Co., Ltd.). White solid (22 mg, 0.05 mmol, 58% yield): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.73 (s, 1H), 8.32 (s, 1H), 7.92 (s, 1H), 7.85 (bs, 1H), 7.59 (d, J=8.0Hz, 1H), 7.30 (t, J=8.0Hz, 1H), 7.19 (s, 1H), 7.11 (d, J=7.6Hz, 1H), 3.95 (s, 3H), 1.37 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 157.1, 156.2, 154.1, 139.5, 134.6, 130.6, 129.9, 124.2, 121.8, 119.7, 109.0, 106.4, 99.5, 84.1, 56.0, 24.8; IR(KBr) 3373, 3246, 2978, 1618, 1526, 1423, 1383, 1315, 1140, 1057, 856 cm^{-1}; MS(APCI) m/z 412 ($[M+H]^+$), 453($[M+H+CH_3CN]$)$^+$); Anal. Calcd for $C_{21}H_{23}BClN_3O_3$: C, 61.27; H, 5.63; N, 10.21; found: C, 61.11; H, 5.62; N, 9.93.

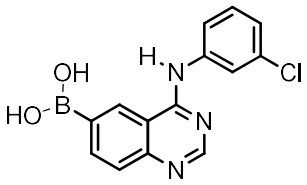
4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-pinacolatoborylquinazoline (6d)



This compound was prepared from **5b** (252 mg, 0.56 mmol), bispinacolatodiboron (170 mg, 0.67 mmol), $PdCl_2$ (11 mg, 0.06 mmol), 1,1'-bis(diphenylphosophino)ferrocene (33 mg, 0.06 mmol), and potassium acetate (165 mg, 1.68 mmol) by the same procedure as described for compound **6c**. White solid (51 mg, 0.12 mmol, 21% yield): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.70 (s, 1H), 8.25 (s, 1H), 7.93

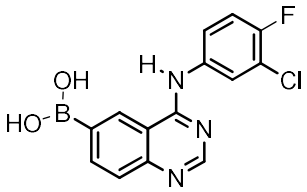
(dd, J=2.8Hz, 6.4Hz,1H), 7.59 (bs, 1H), 7.53－7.57 (m, 1H), 7.19 (s, 1H), 7.16 (t, J=8.4Hz, 1H), 3.96 (s, 3H), 1,38 (s,12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 157.2, 156.6, 156.2, 154.1, 153.3, 134.9, 134.8, 130.4, 124.4, 121.9, 121.8, 121.2, 121.0, 116.7, 116.5, 108.8, 106.4, 84.2, 56.1, 24.8; IR(KBr) 3314, 3121, 2978, 1620, 1501, 1423, 1385, 1223, 1146, 1057, 856 cm^{-1}; MS (ESI) m/z 430 ([M+H]$^+$) ; Anal. Calcd for $C_{21}H_{23}BClN_3O_3$: C, 58.70; H, 5.16; N, 9.78; found: C, 58.41; H, 5.23; N, 9.54.

4-(3-Chloroanilino)-6-dihydroxyborylquinazoline (7a)



To a solution of **6a** (144 mg, 0.38 mmol) in methanol (10 mL) was added a solution of potassium bifluoride (KHF_2; 206 mg, 2.64 mmol) in water (10 mL) and the mixture was stirred at room temperature for 12 h. The solvent was evaporated and acetonitrile, hexane, and phenylboronic acid (139 mg, 1.14 mmol) were added to the residue. The mixture was stirred for 1 h and hexane layer was removed. The resulting acetonitrile layer was evaporated and the residue was purified by thin-layer chromatography on silica gel using dichloromethane/methanol (20:1) to give **7a** (54 mg, 0.18 mmol, 47% yield) as a white solid: ^{1}H NMR (300 MHz; CD_3OD) δ 8.62 (s, 1H), 8.49 (s, 1H), 8.06 (d, *J*=9.0Hz, 1H), 7.89 (s, 1H), 7.59－7.66 (m, 2H), 7.27 (t, *J*=9.0Hz, 1H), 7.07 (d, *J*=9.0Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.3, 155.9, 151.1, 141.8, 139.4, 135.5, 131.1, 129.8, 128.8, 126.8, 125.6, 124.0, 122.3, 116.2; IR(KBr) 3337, 2926, 2322, 1599, 1528, 1435, 1387, 1259, 773, 679 cm^{-1}; MS (ESI) m/z 300 ([$C_{14}H_9ClN_3B(OH)_2$+H]$^+$), 314 ([$C_{14}H_9ClN_3B$(OH) (OMe)+H]$^+$); Anal. Calcd for $C_{14}H_{11}BClN_3O_2$: C, 56.14; H, 3.70; N, 14.03; found: C, 57.31; H, 3.68; N, 14.31.

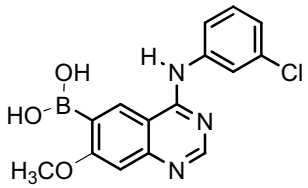
4-(3-Chloro-3-fluoroanilino)-6-dihydroxyborylquinazoline (7b)



This compound was prepared from **6b** (35 mg, 0.09 mmol), KHF_2 (48 mg, 0.61 mmol), and phenylboronic acid (32 mg, 0.26 mmol) by the same procedure as described for compound **7a**. White solid (9 mg, 0.03 mmol, 32% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.85 (s, 1H), 8.68 (s, 1H), 8.30 (d, *J*=8.4 Hz, 1H), 7.82 (dd, *J*=2.4Hz, 6.8Hz, 1H), 7.70 (d, *J*=8.4Hz, 1H), 7.53－7.57 (m, 1H), 7.25 (t, J=8.8Hz, 1H) ; ^{13}C NMR (75 MHz, DMSO-d6) δ 160.0, 156.9, 153.6, 152.3, 140.7, 134.7, 130.8, 126.5, 125.3, 125.2, 120.4, 119.5, 119.3, 117.3, 117.0, 113.4; IR(KBr) 3335, 1618, 1578, 1533, 1499, 1420, 1265, 779 cm^{-1}; MS (ESI) m/z 318 ([$C_{14}H_9ClFN_3B(OH)_2$+H]$^+$), 332([$C_{14}H_9ClFN_3B$(OH)(OMe)+H]$^+$); Anal. Calcd for $C_{14}H_{10}BClFN_3O_2$: C, 52.96; H, 3.17; N, 13.23;

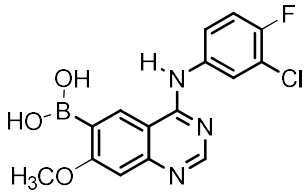
found: C, 52.48; H, 3.20; N, 13.35.

4-(3-Chloroanilino)-7-methoxy-6-dihydroxyborylquinazoline (7c)



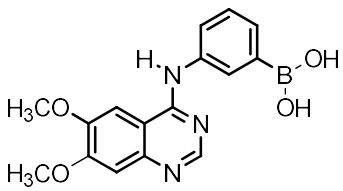
This compound was prepared from **6c** (22 mg, 0.05 mmol), KHF_2 (29 mg, 0.37 mmol), and phenylboronic acid (26 mg, 0.21 mmol) by the same procedure as described for compound **7a**. White solid (8 mg, 0.02 mmol, 48% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.41 (s, 1H), 8.20 (bs, 1H), 7.85 (t, J=2.0Hz, 1H), 7.56 (qd, J=0.8Hz, 8.0Hz, 1H), 7.24 (t, J=8.0Hz, 1H), 7.04 (s, 1H), 7.04 (dq, J=0.8Hz, 8.0Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.9, 156.2, 153.9, 141.7, 138.1, 135.2, 130.9, 125.1, 123.7, 121.9, 110.9, 105.2, 102.8, 56.3; IR (KBr) 3547, 3364, 2947, 1624, 1529, 1427, 1227, 1043 cm^{-1}; MS (ESI) m/z 330 ($[C_{15}H_{11}ClN_3OB(OH)_2+H]^+$), 344 ($[C_{15}H_{11}ClN_3OB(OH)(OMe)+H]^+$); Anal. Calcd for $C_{15}H_{13}BClN_3O_3$: C, 54.67; H, 3.98; N, 12.75; found: C, 54.60; H, 3.74; N, 12.73.

4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-dihydroxyborylquinazoline (7d)



This compound was prepared from **6d** (40 mg, 0.09 mmol), KHF_2 (51 mg, 0.65 mmol), and phenylboronic acid (33 mg, 0.27 mmol) by the same procedure as described for compound **7a**. White solid (13 mg, 0.04 mmol, 41% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.39 (s, 1H), 8.18 (bs, 1H), 7.90－7.92 (m, 1H), 7.54－7.58 (m, 1H), 7.14 (t, J=8.8Hz, 1H), 7.04 (s, 1H), 3.89 (s,3H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.7, 157.9, 155.7, 154.7, 152.3, 136.9, 126.3, 124.5, 124.4, 121.5, 121.3, 117.6, 117.3, 110.4, 104.5, 56.4; IR (KBr) 3368, 3121, 2930, 2320 1624, 1501, 1423, 1223, 1043 cm^{-1}; MS (ESI) m/z 348 ($[C_{15}H_{10}ClFN_3OB(OH)_2+H]^+$), 362 ($[C_{15}H_{10}ClFN_3OB(OH)(OMe)+H]^+$); Anal. Calcd for $C_{15}H_{12}BClFN_3O_3$: C, 51.84; H, 3.48; N, 12.09; found: C, 51.90; H, 3.55; N, 11.89.

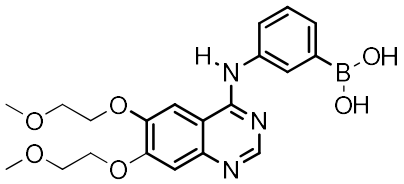
4-(3-Dihydroxyborylanilino)-6,7-dimethoxyquinazoline (9a)



To a solution of **8a** (97 mg, 0.43 mmol) in IPA (3 mL) were added 3-aminophenylboronic acid

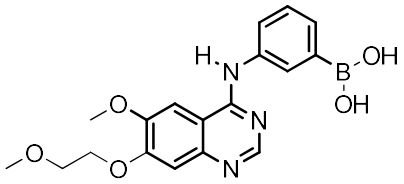
monohydrate (74 ml, 0.48 mmol) and conc. HCl (1 mL). The mixture was stirred at room temperature for 6 h. The precipitate was filtered, washed with IPA and dried in vacuo to give the hydrochloride salt of **9a**, which was treated with aqueous $NaHCO_3$ (1N) to afford **9a** (125 mg, 0.38 mmol, 88% yield) as a white solid: ^{1}H NMR (400 MHz; CD_3OD) δ 8.28 (s, 1H), 7.83 (s, 1H), 7.66 (m, 2H), 7.39 (br, 1H), 7.31 (t, *J*=3.6Hz), 7.05 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.6, 156.4, 153.4, 151.0, 146.5, 139.3, 131.2, 129.8, 129.0, 126.3, 110.2, 106.4, 102.4, 56.8, 56.5; IR (KBr) 3283, 2939, 1624, 1576, 1510, 1242, 1144, 1070, 993 cm^{-1}; MS (ESI) m/z 326 ($[C_{16}H_{14}N_3O_2B(OH)_2+H]^+$), 340 ($[C_{16}H_{14}N_3O_2B(OH)(OMe)+H]^+$); Anal. Calcd for $C_{16}H_{16}BN_3O_4$: C, 59.11; H, 4.96; N, 12.92; found: C, 58.94; H, 5.01; N, 12.67.

4-(3-Dihydroxyborylanilino)-6,7-bis(2-methoxyethoxy)quinazoline (9b)



This compound was prepared from **8b** (111 mg, 0.35 mmol) and 3-aminophenylboronic acid monohydrate (61 ml, 0.39 mmol) by the same procedure as described for compound **9a**. White solid (135 mg, 0.30 mmol, 90% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.27 (s, 1H), 7.83 (s,1H), 7.66－7.69 (m, 2H), 7.39 (m, 1H), 7.31 (t, *J*=7.6Hz, 1H), 7.08(s, 1H), 4.21－4.25 (m, 4H), 3.75－3.79 (m, 4H), 3.39 (s, 3H), 3.38 (s, 3H) ; ^{13}C NMR (100 MHz, CD_3OD) δ 158.5, 155.8, 153.8, 150.2, 147.1, 139.4, 131.1, 129.7, 129.0, 126.3, 110.4, 108.0, 104.0, 71.9, 71.7, 69.9, 69.5, 59.5; IR (KBr) 3364, 2936, 1578, 1508, 1431, 1246, 1123 cm^{-1}; MS(ESI) m/z 428 ($[C_{20}H_{23}N_3O_4B(OH)(OMe)+H]^+$), 450 ($[C_{20}H_{23}N_3O_4B(OH)(OMe)+Na]^+$); Anal. Calcd for $C_{16}H_{16}BN_3O_4$: C, 58.13; H, 5.85; N, 10.17; found: C, 58.33; H, 5.85; N, 10.25.

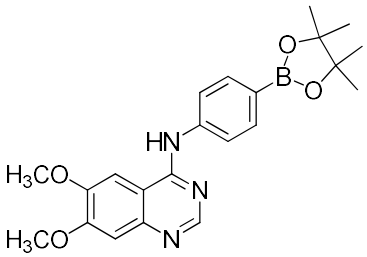
4-(3-Dihydroxyborylanilino)-6-methoxy-7-(2-methoxyethoxy)quinazoline (9c)



This compound was prepared from **8c** (56 mg, 0.21 mmol) and 3-aminophenylboronic acid monohydrate (32 mg, 0.23 mmol) by the same procedure as described for compound **9a**. White solid (39 mg, 0.11 mmol, 50% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.19 (s, 1H), 7.83 (s, 1H), 7.62 (d, J=8.0Hz, 1H), 7.50 (s, 1H), 7.43 (d, *J*=7.2Hz, 1H), 7.25 (t, *J*=8.0Hz, 1H), 6.92 (S, 1H), 4.09－4.11 (m, 2H), 3.86 (s, 3H), 3.68－3.71 (m, 2H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.6, 155.6, 153.8, 151.1, 147.2, 139.4, 131.1, 129.8, 129.0, 126.2, 110.5, 107.9, 102.7, 71.7, 69.4, 59.3, 56.8; IR (KBr) 3344, 2936, 1624, 1578, 1508, 1427, 1246, 1123, 710, MS (ESI) m/z 370 ($[C_{16}H_{14}N_3O_2B(OH)_2+H]^+$), 384 ($[C_{16}H_{14}N_3O_2B(OH)(OMe)+H]^+$), 392 ($[C_{16}H_{14}N_3O_2B(OH)_2+Na]^+$),

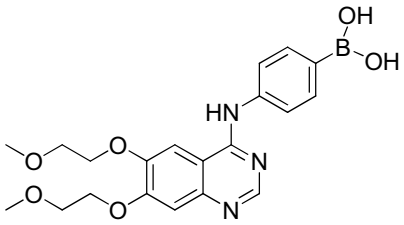
406 ($[C_{16}H_{14}N_3O_2B(OH)(OMe)+Na]^+$); Anal. Calcd for $C_{18}H_{20}BN_3O_5$: C, 58.56; H, 5.46; N, 11.38; found: C, 58.30; H, 5.39; N, 11.31.

4-(4-Pinacolatoboryl)-6,7-dimethoxyquinazoline (11a)



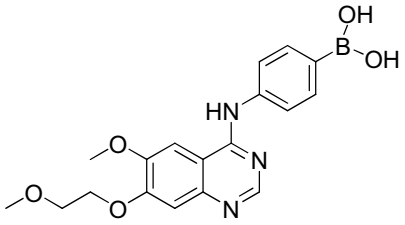
To a solution of **8a** (178 mg, 0.79 mmol) in IPA (12 mL) was added pinacolato 3-aminophenylboronate (173 ml, 0.79 mmol) and the mixture was stirred under reflux for 24 h. After cooled to room temperature, the solvent was removed and the resulting solid was washed with CH_2Cl_2 and dried in vacuo to give **11a** (256 mg, 0.50 mmol, 63% yield) as a white solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.17 (s, 1H), 8.10(s, 1H), 7.96 (d, *J*=8.8Hz, 2H), 7.82 (d, *J*=8.4, 2H), 7.18 (s, 1H), 4.23 (s, 3H), 3.79 (s, 3H), 1.35 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.9, 150.7, 146.5, 139.1, 135.3, 134.9, 123.1, 107.3, 104.2, 99.2, 83.9, 77.2, 57.8, 56.8, 24.8; IR (KBr) 3337, 2978, 2361, 1634, 1514, 1360, 1279, 1144, 1092 cm^{-1}; MS (ESI) m/z 408 ($[M+H]^+$) ; Anal. Calcd for $C_{22}H_{26}BN_3O_4$: C, 64.88; H, 6.43; N, 10.32; found: C, 65.12; H, 6.49; N, 10.39.

4-(4-Dihydroxyboryl)-6,7-bis(2-methoxyethoxy)quinazoline (12b)



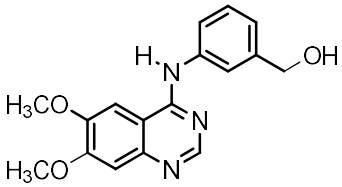
This compound was prepared from **8b** (42 mg, 0.14 mmol) and pinacolato 3-aminophenylboronate (33 ml, 0.15 mmol) by the same procedure as described for compound **9a**. White solid (11 mg, 0.03 mmol, 19% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.29 (s,1H), 7.67 (s, 1H), 7.63 (m, 4H), 7.06 (s, 1H), 4.18－4.24 (m, 4H), 3.74－3.77 (m, 4H), 3.38 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.6, 156.1, 154.0, 150.5, 147.7, 135.5, 122.7, 110.8, 104.4, 72.0, 71.8, 70.1, 69.7, 59.5(C2); IR(KBr) 3368, 2932, 2363, 1508, 1425, 1244, 1123 cm^{-1}; MS (ESI) m/z 414 ($[C_{20}H_{23}N_3O_4B(OH)_2+H]^+$), 428 ($[C_{20}H_{23}N_3O_4B(OH)(OMe)+H]^+$), 450 ($[C_{20}H_{23}N_3O_4B(OH)(OMe)+Na]^+$); Anal. Calcd for $C_{16}H_{16}BN_3O_4$: C, 58.13; H, 5.85; N, 10.17; found: C, 58.40; H, 6.02; N, 9.91.

4-(4-Dihydroxyboryl)-6-methoxy-7-(2-methoxyethoxy)quinazoline (12c)



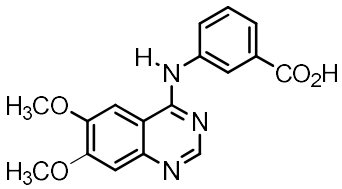
This compound was prepared from **8c** (92 mg, 0.34 mmol) and pinacolato 3-aminophenylboronate (83 ml, 0.37 mmol) by the same procedure as described for compound **9a**. White solid (48 mg, 0.13 mmol, 38% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.30 (s,1H), 7.66 (s, 1H), 7.62 (br, 4H), 7.06 (s, 1H), 4.19－4.21 (m, 2H), 3.93 (s, 3H), 3.75－3.77 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.4, 155.6, 153.8, 151.1, 147.4, 141.5, 135.4, 122.6, 110.7, 107.9, 102.7, 71.7, 69.4, 59.3, 56.8; IR (KBr) 3385, 2933, 2359, 1624, 1508, 1458, 1420, 1339, 1244 cm^{-1}; MS (ESI) m/z; 370 ($[C_{16}H_{14}N_3O_2B(OH)_2+H]^+$), 384 ($[C_{16}H_{14}N_3O_2B(OH)(OMe)+H]^+$), 392 ($[C_{16}H_{14}N_3O_2B(OH)_2+Na]^+$), 406 ($[C_{16}H_{14}N_3O_2B(OH)(OMe)+Na]^+$); Anal. Calcd for $C_{18}H_{20}BN_3O_5$: C, 58.56; H, 5.46; N, 11.38; found: C, 58.59; H, 5.36; N, 11.26.

4-(3-Hydroxymethylanilino)-6,7-dimethoxyquinazoline (13)



This compound was prepared from **8** (73 mg, 0.32 mmol) and 3-aminobenzylalcohol (44 mg, 0.36 mmol) by the same procedure as described for compound **3a**. White solid (103 mg, 0.32 mmol, >99% yield): ^{1}H NMR (400 MHz; CD_3OD) δ 8.57 (s, 1H), 7.92 (s, 1H), 7.63 (s, 1H), 7.53 (d, J=7.6Hz, 1H), 7.37 (t, J=7.6Hz, 1H), 7.24 (d, J=7.6Hz), 7.13 (s, 1H), 4.60 (s, 2H), 4.00 (br, 6H) ; ^{13}C NMR (75 MHz, CD_3OD) δ 158.9, 152.8, 149.5, 144.1, 138.2, 137.0, 130.0, 126.3, 124.5, 124.1, 108.8, 103.9, 100.6, 64.7, 57.4 ; IR (KBr) 3032, 2932, 1636, 1512, 1458, 1281, 1069, 849 cm^{-1}; MS (ESI) m/z 312 ($[M+H]^+$), 334 ($[M+Na]^+$) ; Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50; found: C, 65.68; H, 5.35; N, 13.32.

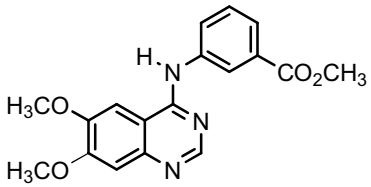
4-(3-Hydroxycarbonyanilino)-6,7-dimethoxyquinazoline (15)



This compound was prepared from **8** (81 mg, 0.36 mmol) and 3-aminobenzoic acid (59 mg, 0.43 mmol) by the same procedure as described for compound **3a**. White solid (117 mg, 0.36 mmol, >99% yield): ^{1}H NMR (400 MHz; DMSO-d_6) δ 11.27 (s, 1H), 8.85 (s, 1H), 8.25 (t, J=2.0Hz, 1H), 8.22 (s, 1H), 8.00 (qd, J=1.2Hz, J=8.0Hz, 1H), 7.86 (td, J=1.6Hz, J=8.0Hz, 1H), 7.61 (t, J=8.0Hz, 1H), 4.01

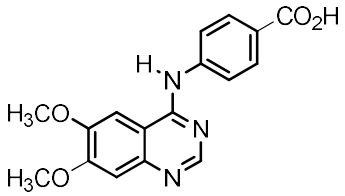
(s, 3H), 3.99 (s, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 158.3, 156.5, 150.4, 148.7, 137.5, 135.7, 131.5, 129.2, 129.1, 127.0, 125.6, 107.5, 104.4, 99.8, 57.3, 56.6; IR (KBr) 3032, 2677, 1709, 1636, 1578, 1516, 1450, 1285, 1072, 984 cm^{-1}; MS(ESI) m/z 326 ([M+H]$^+$), 348 ([M+H+Na])$^+$) ; Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92; found: C, 62.82; H, 4.77; N, 13.18.

4-(3-Methoxycarbonyanilino)-6,7-dimethoxyquinazoline (16)



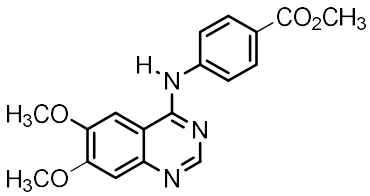
To a solution of **15** (76 mg, 0.23 mmol) in methanol (8 mL) was added conc. HCl (0.05 mL) and the mixture was refluxed for overnight. The solvents were removed in vacuo and the residue was dissolved in ethyl acetate, neutralized with a saturated $NaHCO_3$, washed with brine, and dried over anhydrous $MgSO_4$. The solvents were evaporated in vacuo to give **16** (73 mg, 0.22 mmol, 94% yield): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.70 (s, 1H), 8.21 (s, 1H), 8.18 (d, *J*=8.4Hz, 1H), 7.82 (d, *J*=7.6Hz, 1H), 7.51 (t, *J*=8.0Hz, 1H), 7.29 (s, 1H), 7.22 (bs, 1H), 7.03 (s, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 3.95 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) σ 166.9, 156.2, 154.8, 153.4, 149.6, 147.5, 139.0, 130.8, 129.1, 126.2, 125.0, 122.4, 109.1, 107.8, 99.3, 56.2 (C2), 52.3 ; IR(KBr) 3854, 3736, 3649, 3368, 2951, 2839, 1719, 1624, 1578, 1508, 1431, 1288, 1240, 1001, 849 cm^{-1}; MS(ESI) m/z 340([M+H]$^+$), 362([M+Na]$^+$); Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; found: C, 63.75; H, 4.87; N, 12.50.

4-(4-Hydroxycarbonyanilino)-6,7-dimethoxyquinazoline (17)



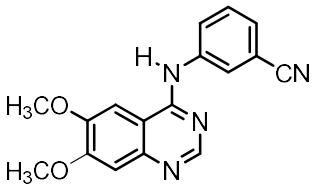
This compound was prepared from **8** (55 mg, 0.24 mmol) and 4-aminobenzoic acid (46 mg, 0.34 mmol) by the same procedure as described for compound **3a**. White solid (77 mg, 0.24 mmol, >99% yield): ^{1}H NMR (300 MHz; DMSO-d_6) δ 11.25 (bs, 1H), 8.87 (s, 1H), 8.26(s, 1H), 8.04 (d, J=8.7Hz, 2H), 7.90 (d, J=8.7Hz, 2H), 7.33 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 158.2, 156.6, 150.5, 149.3, 141.5, 137.0, 130.2, 128.0, 124.1, 107.9, 103.8, 100.6, 57.1, 56.8; IR (KBr) 3020, 1674, 1636, 1512, 1443, 1277, 1231, 841 cm^{-1}; MS (ESI) m/z 326([M+H]$^+$), 348 ([M+H+Na])$^+$) ; Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92; found: C, 62.70; H, 4.81; N, 12.93.

4-(4-Methoxycarbonyanilino)-6,7-dimethoxyquinazoline (18)



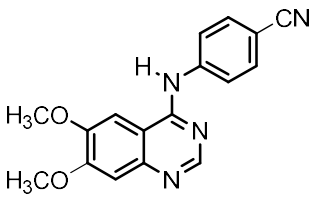
This compound was prepared from **17** (39 mg, 0.12 mmol) by the same procedure as described for compound **16**. White solid (33 mg, 0.10 mmol, 81% yield): ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.74 (s, 1H), 8.05 (d, J=7.6, 2H), 7.84 (d, J=7.2Hz, 2H), 7.77 (bs, 1H), 7.25 (s, 1H), 7.17 (s, 1H), 3.98 (bs, 6H), 3.91 (s, 3H) ; ^{13}C NMR (75 MHz,) δ 166.8, 155.8, 155.0, 153.3, 149.8, 147.7, 143.2, 130.8, 124.9, 120.1, 109.3, 107.8, 99.2, 56.3, 56..2, 52.0 ; IR (KBr) 3749, 3568, 3287, 2951, 1717, 1609, 1512, 1470, 1281, 1246, 1111, 995 cm^{-1}; MS (ESI) m/z 340 ($[M+H]^+$), 362 ($[M+Na]^+$) ; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; found: C, 63.49; H, 5.27; N, 12.39.

4-(3-Cyanoanilino)-6,7-dimethoxyquinazoline (19)



This compound was prepared from **8** (70 mg, 0.31 mmol) and 3-aminobenzonitrile (40 mg, 0.34 mmol) by the same procedure as described for compound **3a**. White solid (92 mg, 0.30 mmol, 97% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.15-8.17 (m, 1H), 7.93-7.97 (m, 2H), 7.57-7.62 (m, 2H), 7.17 (s, 1H), 4.02 (bs, 6H) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 156.6, 150.5, 149.4, 138.4, 130.4, 129.6, 129.3, 127.8, 118.6, 111.7, 107.7, 103.9, 100.7, 57.1, 56.7 ; IR (KBr) 3028, 2577, 2222, 1636, 1574, 1516, 1439, 1285, 1072, 907 cm^{-1}; MS (ESI) m/z 307 ($[M+H]^+$), 329 ($[M+H+Na])^+$) ; Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 66.66; H, 4.61; N, 18.29; found: C, 66.54; H, 4.60; N, 18.57.

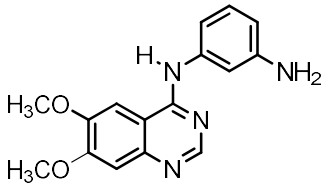
4-(4-Cyanoanilino)-6,7-dimethoxyquinazoline (20)



This compound was prepared from **8** (79 mg, 0.35 mmol) and 4-aminobenzonitrile (46 mg, 0.39 mmol) by the same procedure as described for compound **3a**. White solid (88 mg, 0.29 mmol, 82% yield): ^{1}H NMR (400 MHz,DMSO-d_6) δ 11.58 (s, 1H), 8.90 (s, 1H), 8.41 (s, 1H), 8.05 (d, J=8.0Hz, 2H), 7.93 (d, J=8.4Hz, 2H), 7.37 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.1, 156.7, 150.5, 149.2, 142.0, 137.4, 133.4, 124.5, 119.0, 108.1, 107.7, 104.0, 100.7, 57.2,

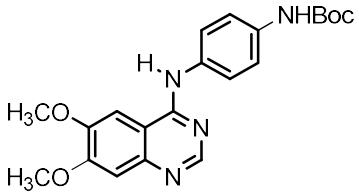
56.7 ; IR (KBr) 3854, 3649, 3032, 2941, 2839, 2228, 1636, 1508, 1435, 1279, 1238, 1069, 854 cm^{-1}; MS (ESI) m/z 307 ($[M+H]^+$), 329 ($[M+H+Na])^+$); Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 66.66; H, 4.61; N, 18.29; found: C, 66.78; H, 4.74; N, 18.59.

4-(3-Aminoanilino)-6,7-dimethoxyquinazoline (21)



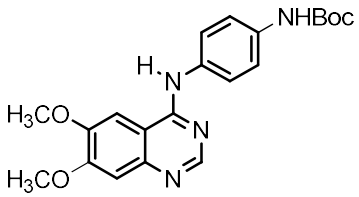
This compound was prepared from **8** (86 mg, 0.38 mmol) and *meta*-phenylenediamine (50 mg, 0.46 mmol) by the same procedure as described for compound **3a**. White solid (17 mg, 0.06 mmol, 17% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.67 (s, 1H), 7.02-7.11 (m, 3H), 6.91 (d, J=8.0Hz, 1H), 6.54 (d, J=8.0, 1H), 3.97 (s, 3H), 3.94 (s, 3H) ; ^{13}C NMR (75 MHz, CD_3CN) δ 157.7, 155.7, 154.0, 150.4, 149.4, 148.2, 141.2, 130.1, 112.4, 111.1, 110.1, 109.4, 108.3, 102.0, 57.0, 56.6; IR (KBr) 3375, 2928, 1624, 1581, 1508, 1458, 1420, 1219, 849 cm^{-1}; MS (ESI) m/z 297 ($[M+H]^+$), 319 ($[M+H+Na])^+$) ; Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 64.85; H, 5.44; N, 18.91; found: C, 64.76; H, 5.53; N, 18.71.

4-(4-*tert*-Butoxycarbonylaminoanilino)-6,7-dimethoxyquinazoline (22)



This compound was prepared from **8** (77 mg, 0.34 mmol) and *N*-Boc-phenylenediamine (78 mg, 0.38 mmol) by the same procedure as described for compound **3a**. White solid (118 mg, 0.30 mmol, 87% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (s, 1H), 7.90 (s, 1H), 7.44 -7.54 (m, 4H), 7.12 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 1.47 (s, 9H) ; ^{13}C NMR (75 MHz, CD_3OD) δ 159.9, 158.8, 155.2, 152.7, 149.5, 139.5, 136.8, 132.5, 126.1, 119.8, 108.7, 103.9, 100.5, 81.1, 57.3 (C2), 28.7 ; IR (KBr) 3422, 2978, 1701, 1636, 1574, 1516, 1435, 1231, 1161, 1069 cm^{-1}; MS (ESI) m/z 379 ($[M+H]^+$), 419 ($[M+H+Na])^+$) ; Anal. Calcd for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13; found: C, 63.54; H, 6.01; N, 14.25.

4-(4-Aminoanilino)-6,7-dimethoxyquinazoline (23)



To a solution of **22** (47 mg, 0.12 mmol) in 1,2-dichloroethane (5 mL) was added trifluoroacetic acid (0.04 mL, 0.48 mmol) and the mixture was stirred at 50 °C for 24 h. The solvents were removed in vacuo and the residue was dissolved in ethyl acetate, neutralized with a saturated $NaHCO_3$, washed with brine, and dried over anhydrous $MgSO_4$. Purification by silica gel column chromatography with dichloromethane/methanol (20:1) to give **23** (36 mg, 0.12 mmol, >99% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.34 (d, J=8.4Hz, 2H), 7.23 (s, 1H), 7.13 (bs, 1H), 7.02 (s, 1H), 6.72 (d, J=8.4Hz, 2H), 4.01 (s, 3H), 3.97 (s, 3H), 3.65 (br, 2H) ; ^{13}C NMR (75 MHz, CD_3CN) δ 157.2, 154.5, 154.0, 149.2, 147.3, 144.0, 129.3, 125.1, 115.6, 108.8, 107.9, 99.6, 56.2 ; IR (KBr) 3383, 1624, 1582, 1516, 1474, 1435, 1246, 853 cm^{-1}; M S(ESI) m/z 297 ($[M+H]^+$) ; Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 64.85; H, 5.44; N, 18.91; found: C, 64.72; H, 5.64; N, 18.84.

Kinase assays. The kinase activity of various tyrosine kinases was determined by ELISA. EIA/RIA stripwell™ plates (Corning) were coated by incubation overnight at 4°C with 100 μL/well of 50 μg/mL poly(Glu:Tyr, 4:1) peptide (Sigma) in PBS. Inhibitors were dissolved in DMSO to make stock solutions (100 μM), which were diluted to be final concentrations at 0.001~1 μM. The kinase reaction was performed in the plates by addition of 50 μL of kinase buffer (50 mM HEPES, 125 mM NaCl, 10 mM $MgCl_2$, pH 7.4) containing ATP, 10 ng of recombinant EGFR, HER2, Flt-1 or KDR (Invitrogen, catalytic domain), and inhibitors. After 20 min, the plates were washed three times with wash buffer (0.1% Tween 20 in PBS) and incubated for 20 min with 50 μL/well of 0.2 μg/mL HRP conjugated anti-phosphotyrosine antibody (Santa Cruz). After two washes, the plates were developed by addition of 50 μL/well tetramethylbenzidine (Sigma) and stopped by addition of 50 μL/well of 2N H_2SO_4. The absorbance at 450 nm was measured by a 96-well plate reader (Tecan).

Cell culture. The human epidermoid carcinoma cell line A431 was obtained from the Cell Resource Center for Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University (Sendai, Japan). The cells were cultured at 37°C under 5% CO2 atmosphere in RPMI 1640 medium (Wako Pure Chemicals, Osaka, Japan) supplemented with 10% fetal bovine serum (FBS, HyClone, Logan, UT), 100 U/mL penicillin, and 100 μg/ml streptomycin (Invitrogen, Carlsbad, CA). The human umbilical vein endothelial cell (HUVEC, Cell Applications) was cultured in endothelial cell growth medium (V2) and subculture reagent kit (Cell Applications). For subsequent experiments, the cells were seeded at a density of 2 x 10^5 cells/ml/well in a 12-well TC plate (Greiner Japan, Tokyo, Japan), and incubated at 37°C for 20 h.

Immunoblot analysis. After stimulation for the specified period, the cells were washed three times with PBS, dipped in 100 μL of ice-cold lysis buffer (20 mM HEPES, pH 7.4, 1% Triton-X 100, 10% glycerol, 1 mM sodium vanadate, 5 μg/mL of leupeptin, and 1 mM EDTA) for 15 min, and disrupted with a Handy Sonic Disrupter, and the lysate was boiled for 5 min in a sample buffer (50 mM Tris, pH 7.4, 4% sodium dodecylsufate (SDS), 10% glycerol, 4% 2-mercaptoethanol, and 0.05 mg/mL of

bromophenol blue) at a ratio of 4:1. The proteins were separated by 10% SDS-polyacrylamide gel electrophoresis and transferred onto a PVDF membrane (Millipore). For the immunoblotting, antibodies used were phospho-EGFR (Tyr1174) antibody (Santa Cruz), EGFR antibody (Santa Cruz), phospho-Akt (Ser473) antibody (Cell Signaling), phospho-p44/42 MAP kinase (Tyr204) antibody (Santa Cruz), phospho-KDR (Tyr1059) antibody (Upstate), KDR antibody (Santa Cruz), and α-tubulin (Santa Cruz). After incubation with HRP-conjugated secondary antibody (Santa Cruz), the blot was reacted with ECL kit (Promega), and the levels of each protein were visualized by a ChemiDoc XRS image analyzer (Bio-Rad).