Supporting Information

Discovery of AZD8931, an equipotent, reversible inhibitor of signalling by EGFR, HER2 and HER3 receptors.

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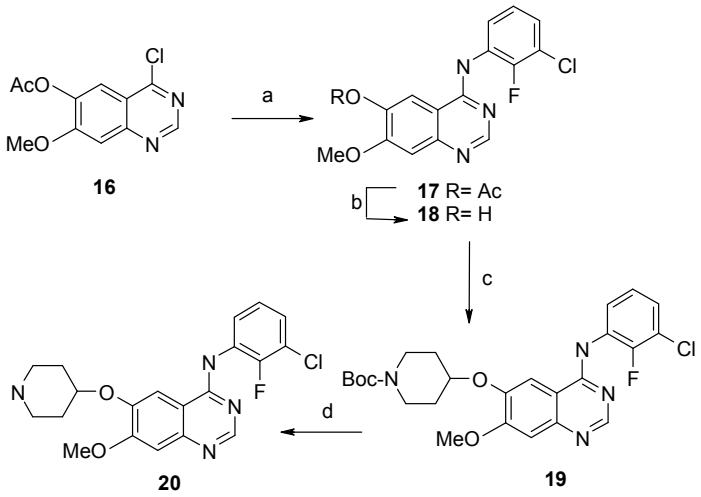
Synthesis of compounds

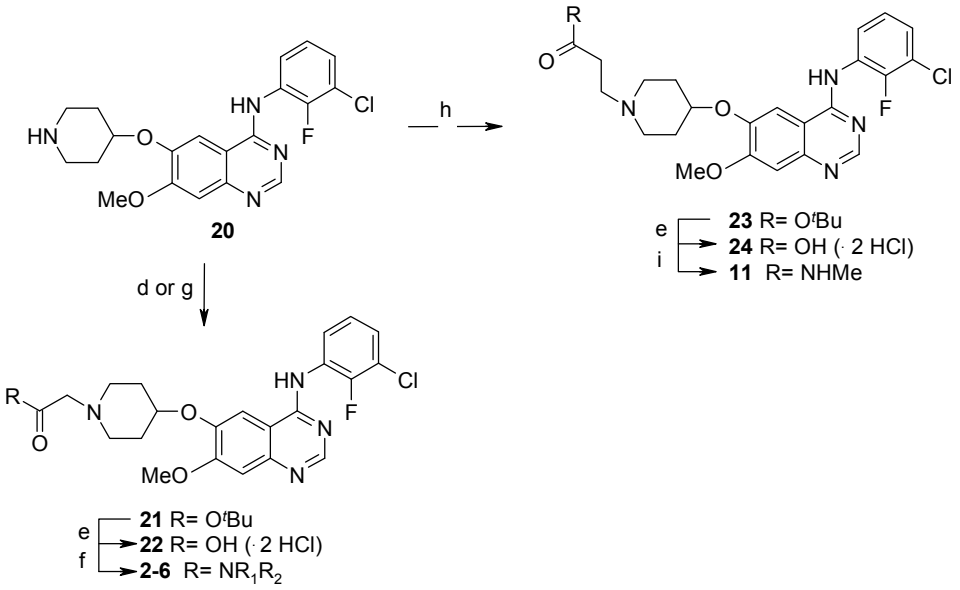
Compounds **2-15** were made according to the Schemes 1-5 below

Scheme 1[a]



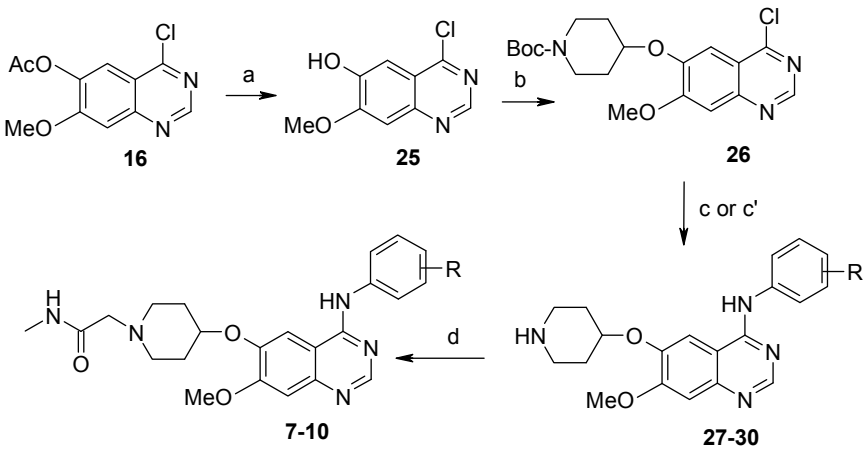
[a] Reagents: (a) 2-F, 3-Cl aniline, *i*PrOH reflux; (b) NH_3/methanol 50°C; (c) 1-Boc-4-MsO-piperidine, CsF, DMA 85°C; (d) TFA, CH_2Cl_2 rt.

Scheme 2[a]



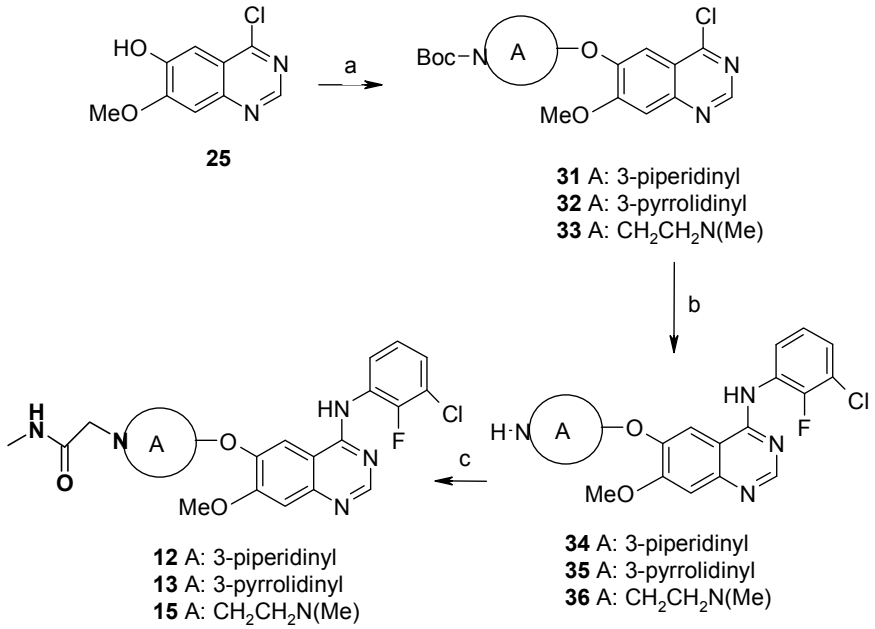
[a] Reagents (d) $ClCH_2CO_2{}^tBu$, KI, K_2CO_3, DMF 70°C (for **21**); (e) HCl, dioxane rt; (f) EDCI, HOBT, R_1R_2NH, CH_2Cl_2, rt (for **3-5**); (g) $BrCH_2CONH_2$, N^iPr_2Et, CH_2Cl_2, rt (for **1**); $ClCH_2CONR_1R_2$, KI, K_2CO_3, CH_3CN (for **2**,**6**); (h) $CH_2{=}CHCO_2{}^tBu$, MeOH; (i) EDCI, HOBT, $MeNH_2$, CH_2Cl_2, rt.

Scheme 3[a]



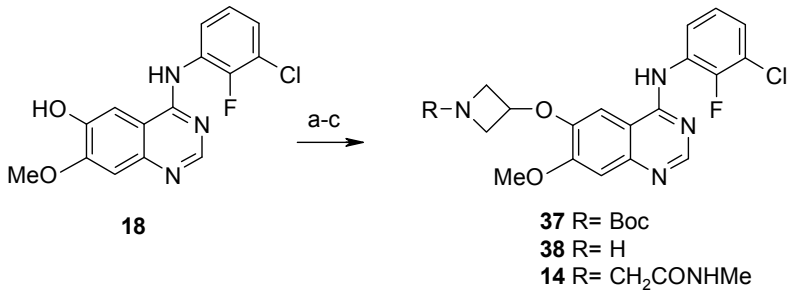
[a] Reagents: (a) NH_3/methanol 10°C; (b) DTAD, PPh_3, 1-Boc-4-OH-piperazine, CH_2Cl_2; (c) aniline, HCl, ^{i}PrOH, 80°C 1 h then TFA rt (for **27-30**); (c') aniline, HCl, *i*PrOH , 80°C 3 h or aniline, HCl, CH_3CN, reflux 3 h; (d) $ClCH_2CONHMe$, KI, K_2CO_3, DMA 70°C.

Scheme 4[a]



[a] Reagents: (a) DTAD or DEAD, PPh_3, alcohol, CH_2Cl_2; (c) 2-F 3-Cl aniline, HCl, CH_3CN, reflux 3 h; (d) $ClCH_2CONHMe$, KI, K_2CO_3, DMA 70°C.

Scheme 5[a]



[a] Reagents: (a) DTAD, PPh_3, 1-Boc-3-OH-azetidine, CH_2Cl_2; (b) TFA, CH_2Cl_2 rt; (c) $ClCH_2CONHMe$, KI, K_2CO_3, DMA 70°C.

Experimental details

All experiments were carried out under an inert atmosphere and at room temperature unless otherwise stated. Flash chromatography was carried out on Merck Kieselgel 50 (Art. 9385). TLCs were performed on precoated silica gel plates (Merck Art. 5715), and the resulting chromatograms were visualized under UV light at 254 nm. Purification by preparative HPLC/MS was done on a Waters LC/MS system using a Waters Symmetry column (C18, 5 µm, 19 mm diameter, 100 mm length) using a mixture of water with 1% acetic acid and acetonitrile (gradient from 5% to 100%) as solvent, unless stated otherwise. The NMR spectra were obtained on a JEOL JNM EX 400 (400 MHz) spectrometer. Chemical shifts are expressed in unit of δ (ppm), and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; br s, broad singlet; m, multiplet. The retention times (t_R) were measured on the LC/MS Waters 2790 / ZMD Micromass system equiped with a Waters Symmetry column (C18, 3.5µM, 4.6 x 50 mm); detection UV 254 nM and MS; elution: flow rate 2.5 ml/min, linear gradient from 95% water - 5% methanol containing 5% formic acid to 40% water - 55% acetonitrile - 5% methanol containing 5% formic acid over 3 min; then linear gradiant to 95% acetonitrile - 5% methanol containing 5% formic acid over 1 min. Mass spectrometry was done on the analytical Waters LC/MS system described above with positive and negative ion data collected automatically. NMR and mass spectra were run on isolated intermediates and final products and are consistent with the proposed structures. For the microanalysis, all the adducts mentioned were measured: water was measured by the Karl-Fisher method using a Mettler DL 18; HCl content was determined on a Metrohm 686 by titration using silver nitrate solution and the organic adducts were measured by ^{1}H NMR.
The following abbreviations have been used: Boc: *tert*-butoxycarbonyl; DEAD: diethylazodicarboxylate; DTAD: di-*tert*-butylazodicarboxylate; DMA: *N*,*N*-dimethylacetamide; DMF: *N*,*N*-dimethylformamide; DMSO: dimethylsulfoxide; TFA: trifluoracetic acid.

6-Acetoxy-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (17). 6-Acetoxy-4-chloro-7-methoxyquinazoline **16** [prepared as described in Example 25-5 of Int. Pat. Appl. WO2001/66099] (6.00 g, 23.8 mmol) and 3-chloro-2-fluoroaniline (3.46 g, 23.8 mmol) were suspended in isopropanol (200 mL). The mixture was heated to 80°C under reflux for 3 h. The solvent was evaporated; the residue was crystallised from acetonitrile, giving 8.16 g of **17** as the hydrochloride salt (92%). ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H), 4.00 (s, 3H), 7.34 (m, 1H), 7.48 (s, 1H), 7.52 (m, 1H), 7.61 (m, 1H), 8.62 (s, 1H), 8.86 (s, 1H). MS-ESI *m/z* 362 $[MH]^+$.
4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (18). 6-Acetoxy-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline hydrochloride **17** (8.72 g, 21.9 mmol) was dissolved in methanol (200 mL). Concentrated aqueous ammonia (15 mL) was added, and the solution heated to 50°C with stirring for 2 h, causing precipitation of a cream coloured solid. The solid was collected by filtration, washed with diethyl ether (3x 200 mL), and dried under vacuum at 60°C over diphosphorous pentoxide, giving 5.40 g of **18** (77%). ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 3H), 7.19 (s, 1H), 7.23 (dd, 1H), 7.42 (dd, 1H), 7.50 (dd, 1H), 7.64 (s, 1H), 8.32 (s, 1H), 9.43 (s, 1H), 9.67 (br s, 1H). MS-ESI *m/z* 320 $[MH]^+$.
6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (19). 4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline **18** (1.87g, 5.85 mmol) was dissolved in DMA (50 ml). 1-*tert*-butoxycarbonyl-4-methanesulfonyloxypiperidine [prepared as in Chemical & Pharmaceutical Bulletin 2001, **49(7)**, 822-829] (490 mg, 1.76 mmol) and cesium fluoride (890 mg, 5.85 mmol) were added, and the mixture was heated to 85°C with stirring. At intervals of 2 h, 4 h and 6 h, 1-*tert*-butoxycarbonyl-4-methanesulfonyloxypiperidine and cesium fluoride were added in the above quantities to the reaction mixture. Heating was continued at 85°C for a further 6 h after the final addition. The solvent was evaporated, and the residue was partitioned between dichloromethane (150 mL) and water (150 mL). The aqueous layer was extracted with dichloromethane (4x 100 mL). The combined organic fractions were dried over magnesium sulfate and evaporated. The residue was purified by chromatography, eluting with 0 to 2.5% (7:1 methanol / concentrated aqueous ammonia) in dichloromethane, giving 2.4 g of **19** (58%, allowing for 2.3 equivalents of residual DMA). ^{1}H NMR (DMSO-d_6): δ 1.40 (s, 9H), 1.60-1.65 (m, 2H), 1.95-2.00 (m, 2H), 3.20-3.25 (m, 2H), 3.65-3.70 (m, 2H), 3.92 (s, 3H), 4.68 (m, 1H), 7.21 (s, 1H), 7.27 (dd, 1H), 7.47 (m, 1H), 7.51 (dd, 1H), 7.85 (s, 1H), 8.36 (s, 1H), 9.53 (s, 1H). MS-ESI *m/z* 503 $[MH]^+$.
4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline (20). 6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline **19** (350 mg, 0.70 mmol) was dissolved in TFA (5 mL), and the solution stood for 2 h. The excess TFA was evaporated, and the residue was azeotroped twice with dichloromethane. The residue was purified by chromatography, eluting with 0 to 4% (7:1 methanol / concentrated aqueous ammonia) in dichloromethane. Evaporation of the appropriate fractions gave 270 mg of **20** (96%). ^{1}H NMR (DMSO-d_6): δ 1.53-1.64 (m, 2H), 2.00-2.05 (m, 2H), 2.64-2.72 (m, 2H),

3.00-3.07 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 7.20 (s, 1H), 7.26 (m, 1H), 7.47 (dd, 1H), 7.50 (dd, 1H), 7.82 (s, 1H), 8.34 (s, 1H), 9.56 (s, 1H). MS-ESI *m/z* 403 $[MH]^+$.

6-{[1-(Carbamoylmethyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (1). 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline **20** (70 mg, 0.17 mmol) was dissolved in dichloromethane (10 mL), and diisopropylethylamine (45 μL, 0.26 mmol), then 2-bromoacetamide (36 mg, 0.26 mmol) were added. The solution stirred for 16 h at ambient temperature. The solvent was evaporated, and the residue purified by chromatography, eluting with 0 to 3% (7:1 methanol / concentrated aqueous ammonia) in dichloromethane. After evaporation of the solvents, the residue was crystallised from acetonitrile to 48 mg of **1** (60%). ^{1}H NMR (DMSO-d_6): δ 1.70-1.84 (m, 2H), 1.98-2.09 (m, 2H), 2.38 (m, 2H), 2.70-2.80 (m, 2H), 2.89 (s, 2H), 3.92 (s, 3H), 4.54 (m, 1H), 7.08 (br s, 2H), 7.20 (s, 1H), 7.26 (m, 1H), 7.47 (m, 1H), 7.51 (m, 1H), 7.80 (s, 1H), 8.35 (s, 1H), 9.53 (s, 1H). MS-ESI *m/z* 460 $[MH]^+$. Anal. ($C_{22}H_{23}ClFN_5O_3 \cdot 0.3\ H_2O$) C, H, N. Found C, 56.77; H, 4.92; N, 14.86; Requires C, 56.79; H, 5.11; N, 15.05%.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (2). 2-Chloro-*N*-methylacetamide (32 mg, 0.3 mmol) was added dropwise to a mixture of **20** (120 mg, 0.3 mmol), potassium iodide (16 mg, 0.1 mmol), and potassium carbonate (50 mg, 0.36 mmol) in acetonitrile (5 mL). The mixture was heated at reflux for 1 h. After evaporation of the solvents under vacuum, the residue was taken up in dichloromethane. The organic solution was washed with water and brine, dried over magnesium sulfate. After evaporation of the solvents under vacuum, the residue was purified by chromatography on silica gel (eluant: 1% to 2% 7N methanolic ammonia in dichloromethane) to give 85 mg of **2** as a white solid (60%).^{1}H NMR ($CDCl_3$): δ 1.98 (m, 2H), 2.08 (m, 2H), 2.46 (m, 2H), 2.85 (m, 2H), 2.87 (d, 3H), 3.07 (s, 2H), 4.02 (s, 3H), 4.49 (m, 1H), 7.16 (m, 4H), 7.31 (m, 2H), 8.49 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* MH^+ 474 $[MH]^+$. Anal. ($C_{23}H_{25}ClFN_5O_3 \cdot 0.21\ H_2O$) C, H, N. Found C, 57.88; H, 5.45; N, 14.67; Requires C, 57.83; H, 5.36; N, 14.66%.

A similar procedure was used to prepare **6**

4-(3-Chloro-2-fluoroanilino)-6-{[1-(*N*,*N*-dimethylcarbamoylmethyl)piperidin-4-yl]oxy}-7-methoxyquinazoline (6). 87 mg, 60%; Starting halide: 2-chloro-*N*,*N*-dimethylacetamide. ^{1}H NMR ($CDCl_3$): δ 1.97 (m, 2H), 2.09 (m, 2H), 2.47 (m, 2H), 2.87 (m, 2H), 2.97 (s, 3H), 3.10 (s, 3H), 3.24 (s, 2H), 4.01 (s, 3H), 4.47 (m, 1H), 7.16 (m, 2H), 7.20 (s, 1H), 7.29 (s, 1H), 7.37 (br s, 1H), 8.45 (m, 1H), 8.69 (s, 1H). MS-ESI *m/z* 488 $[MH]^+$. LC t_R: 2.00 min.

***tert*-Butyl [4-({4-(3-chloro-2-fluoroanilino)-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]acetate (21).** *tert*-Butyl chloroacetate (1.43 ml, 10 mmol) was added dropwise to a mixture of **20** (4.02 g, 10 mmol), potassium iodide (1.66 g, 10 mmol) and potassium carbonate (1.66 g, 12 mmol) in DMA (50 ml). The mixture was heated at 70°C for 1 h. After evaporation of the solvents under vacuum, the residue was triturated in water. The resulting solid was filtered, washed with water and purified by chromatography on silica gel (eluant: 2% 7N methanolic ammonia in dichloromethane) to give 3.0 g of **21** (60%). ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H), 2.01 (m, 2H), 2.10 (m, 2H), 2.56 (m, 2H), 2.89 (m, 2H), 3.19 (s, 2H), 4.01 (s, 3H), 4.49 (m, 1H), 7.16 (m, 3H), 7.29 (m, 2H), 8.48 (m, 1H), 8.70 (s, 1H). MS-ESI *m/z* 517 $[MH]^+$.

[4-({4-(3-Chloro-2-fluoroanilino)-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]acetic acid (22). A suspension of **21** (3.0 g, 5.8 mmol) in a solution of 4N hydrogen chloride in dioxane (40 mL) was stirred at room temperature for 3 h. The solvents were evaporated under high vacuum. The residue was triturated in ether, filtered and washed with ether to give 3.1 g of **22** as the dihydrochloride salt (100%).^{1}H NMR (DMSO-d_6): δ 2.16 (m, 2H), 2.34 (m, 2H), 3.40 (m, 4H), 4.03 (s, 3H), 4.21 (s, 2H), 4.92 (br s, 1H), 7.38 (m, 1H), 7.55 (m, 1H), 7.64 (m, 2H), 8.38 (s, 1H), 8.87 (s, 1H). MS-ESI *m/z* 461 $[MH]^+$.

A similar procedure was used for **3-[4-({4-(3-Chloro-2-fluoroanilino)-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]propionic acid (24).** 3.70 g as the dihydrochloride salt, 97% from tert-butyl 3-[4-({4-(3-Chloro-2-fluoroanilino)-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]propionate **(23)**). ^{1}H NMR (DMSO-d_6 + K_2CO_3): δ 1.64 (m, 2H), 2.06 (m, 4H), 2.20 (m, 2H), 2.53 (m, 2H), 2.76 (m, 2H), 3.92 (s, 3H), 4.52 (m, 1H), 7.16 (s, 1H), 7.23 (m, 1H), 7.42 (m, 1H), 7.55 (m, 1H), 8.03 (m, 1H), 8.31 (s, 1H). MS-ESI *m/z* 475 $[MH]^+$.

***tert*-Butyl [4-({4-(3-chloro-2-fluoroanilino)-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]propionate (23).** A mixture of 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline **20** (4.03 g, 10 mmol) and *tert*-butyl acrylate (1.61 mL, 11 mmol) in methanol (100 mL) was stirred at room temperature for 18 h. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 3% 7N methanolic ammonia in dichloromethane) to give 4.20 g of **23** (79%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 1.95 (m, 2H), 2.06 (m, 2H), 2.34 (m, 2H), 2.44 (t, 2H), 2.71 (t, 2H), 2.83 (m, 2H), 4.01 (s, 3H), 4.48 (m, 1H), 7.16 (m, 3H), 7.29 (s, 1H), 7.38 (br s, 1H), 8.50 (m, 1H), 8.70 (s, 1H). MS-ESI *m/z* 531 $[MH]^+$.

4-(3-Chloro-2-fluoroanilino)-6-{[1-(N-ethylcarbamoylmethyl)piperidin-4-yl]oxy}-7-methoxyquinazoline (3). A suspension of **22** as the dihydrochloride salt (212 mg, 0.4 mmol), 1-hydroxybenzotriazole (66 mg, 0.48 mmol), diisopropylethylamine (0.14 mL, 0.8 mmol), ethylamine (0.24 mL, 0.48 mmol, 2M in THF) and 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (92 mg, 0.48 mmol) in dichloromethane (5 mL) was stirred for 2 h. The mixture was washed with water, 10% aqueous sodium bicarbonate and brine and dried over magnesium sulfate. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 2-3% 7N methanolic ammonia in dichloromethane) and triturated in acetonitrile to give 47 mg of **3** (24%). ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H), 1.98 (m, 2H), 2.09 (m, 2H), 2.45 (m, 2H), 2.87 (m, 2H), 3.05 (s, 2H), 3.33 (m, 2H), 4.02 (s, 3H), 4.49 (m, 1H), 7.16 (m, 4H), 7.30 (s, 1H), 7.33 (s br, 1H), 8.48 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* 488 $[MH]^+$. Anal. ($C_{24}H_{27}ClFN_5O_3 \cdot 0.5\ H_2O$) C, H, N. Found C, 57.72; H, 5.55; N, 14.10; Requires C, 58.00; H, 5.68; N, 14.09%.

A similar procedure was used to prepare **4, 5**, **11**.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-(2-methoxyethyl)carbamoylmethyl)piperidin-4-yl]oxy}quinazoline (4). 57 mg, 28%; Starting amine: 2-methoxyethylamine. ^{1}H NMR ($CDCl_3$): δ 1.98 (m, 2H), 2.09 (m, 2H), 2.45 (m, 2H), 2.87 (m, 2H), 3.07 (s, 2H), 3.38 (s, 3H), 3.48 (s, 4H), 4.02 (s, 3H), 4.49 (m, 1H), 7.16 (m, 3H), 7.31 (m, 2H), 7.48 (br s, 1H), 8.49 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* 518 $[MH]^+$. Anal. ($C_{25}H_{29}ClFN_5O_4 \cdot 0.8\ H_2O \cdot 0.05\ CH_3CN$) C, H, N. Found C, 56.49; H, 5.70; N, 13.30; Requires C, 56.41; H, 5.80; N, 13.23%.

4-(3-Chloro-2-fluoroanilino)-6-{[1-(*N*-isopropylcarbamoylmethyl)piperidin-4-yl]oxy}-7-methoxyquinazoline (5). 70 mg, 35%; Starting amine: isopropylamine. ^{1}H NMR ($CDCl_3$): δ 1.18 (d, 6H), 1.98 (m, 2H), 2.11 (m, 2H), 2.43 (m, 2H), 2.88 (m, 2H), 3.02 (s, 2H), 4.02 (s, 3H), 4.10 (m, 1H), 4.49 (m, 1H), 6.97 (m, 1H), 7.16 (m, 2H), 7.31 (m, 2H), 8.49 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* 502 $[MH]^+$. Anal. ($C_{25}H_{29}ClFN_5O_3$) C, H, N. Found C, 59.46; H, 5.89; N, 14.06; Requires C, 59.82; H, 5.82; N, 13.95%.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylethyl)piperidin-4-yl]oxy}quinazoline (11). 200 mg, 68% from **24**. ^{1}H NMR ($CDCl_3$): δ 1.97 (m, 2H), 2.12 (m, 2H), 2.36 (m, 2H), 2.42 (t, 2H), 3.67 (t, 2H), 2.80 (d, 3H), 2.91 (m, 2H), 4.02 (s, 3H), 4.50 (m, 1H), 7.16 (m, 3H), 7.31 (s, 2H), 8.03 (m, 1H), 8.50 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* 488 $[MH]^+$. Anal. ($C_{24}H_{27}ClFN_5O_3$) C; H, N. Found C, 58.67; H, 5.40; N, 14.33; Requires C, 59.08; H, 5.58; N, 14.35%.

4-Chloro-6-hydroxy-7-methoxyquinazoline (25). 6-Acetoxy-4-chloro-7-methoxyquinazoline **16** (10.0 g, 39.6 mmol) was added in portions to a stirred 7N methanolic ammonia solution (220 mL) cooled to 10°C in an ice/water bath. After stirring for 1 h, the precipitate was filtered, washed with diethyl ether and dried thoroughly under high vacuum to give 5.65 g of **25** (68%). ^{1}H NMR (DMSO-d_6): δ 3.96 (s, 3H); 7.25 (s, 1H); 7.31 (s, 1H); 8.68 (s, 1H). MS-ESI *m/z* 211 $[MH]^+$.

6-[1-(*tert*-Butoxycarbonyl)piperidin-4-yloxy]-4-chloro-7-methoxyquinazoline (26). DTAD (9.22 g, 40 mmol) in dichloromethane (20 mL) was added slowly to a stirred suspension of 4-chloro-6-hydroxy-7-methoxyquinazoline **25** (5.63 g, 26.7 mmol), 4-hydroxy-1-*tert*-butoxycarbonylpiperidine (8.06 g, 40 mmol) and triphenylphosphine (10.5 g, 40 mmol) in dichloromethane (100 mL) at 5°C. The reaction mixture was allowed to warm to room temperature for 16 h, then evaporated under vacuum and adsorbed onto silica and the product was eluted with isohexane/ethyl acetate/triethylamine (75/24/1 followed by 70/29/1) to give 10.3 g of **26** (98%). ^{1}H NMR (DMSO-d_6): δ 1.40 (s, 9H), 1.56-1.69 (m, 2H), 1.93-2.04 (m, 2H), 3.20-3.31 (m, 2H), 3.60 -3.70 (m, 2H), 4.00 (s, 3H), 4.89 (m, 1H), 7.45 (s, 1H), 7.50 (s, 1H), 8.86 (s, 1H). MS-ESI *m/z* 394 $[MH]^+$.

A similar procedure was used for the synthesis of **6-[1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yloxy]-4-chloro-7-methoxyquinazoline 32** (using *N*-*tert*-butoxycarbonyl-3-hydroxypyrrolidine [Nutt, Ruth F.; Joullie, Madeleine M. *J. Am. Chem. Soc*. **1982**, *104*, 5852-5853]), **6-[2-(N-*tert*-Butoxycarbonyl-N-methylamino)ethoxy]-4-chloro-7-methoxyquinazoline 33** (using 2-[*N*-(*tert*-butoxycarbonyl)-N-methylamino]ethanol [Basel, Yochai; Hassner, Alfred *J. Org. Chem.* **2000**, *65*, 6368 - 6380.]).

6-[1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yloxy]-4-chloro-7-methoxyquinazoline (32). 1.40 g (containing unidentified impurities, not purified further and used as it was for the synthesis of **35**) from **36** and N-tert-butoxycarbonyl-3-hydroxypyrrolidine. LC t_R: 3.44 min. MS-ESI *m/z* 380 $[MH]^+$.

6-[2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)ethoxy]-4-chloro-7-methoxyquinazoline (33). 17.0 g, 93% from **36** and 2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethanol. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 3.06 (s, 3H), 3.75 (m, 2H), 4.04 (s, 3H), 4.30 (m, 2H), 7.3 (s, 1H); 7.4 (s, 1H); 8.85 (s, 1H). MS-ESI *m/z* 368 $[MH]^+$.

6-[1-(*tert*-Butoxycarbonyl)piperidin-3-yloxy]-4-chloro-7-methoxyquinazoline (31).

DEAD (9.41 mL, 40% solution in toluene, 20.7 mmol) was added to a mixture of **25** (2.90 g, 1.37 mmol), triphenylphosphine (5.43 g, 20.7 mmol) and *tert*-butoxycarbonyl-3-hydroxypiperidine (4.15 g, 20.7 mmol) in dichloromethane (75 mL). The resulting solution was heated to 40ºC for 6 h, and then allowed to stand 18 h at room temperature. This was purified by flash column chromatography eluting with isohexane (79%), acetone (20%), and triethylamine (1%) to give 2.47 g of **31** (53%). ^{1}H NMR ($CDCl_3$): δ 1.5 (m, 9H); 1.6 (m, 1H); 1.9 (m,

2H); 2.1 (m, 1H); 3.5 (m, 1H); 3.6 (m, 1H); 4.0 (s, 3H); 4.2-3.9 (m, 2H); 4.5 (m, 1H); 7.3 (s, 1H); 7.4 (s, 1H); 8.9 (s, 1H). MS-ESI *m/z* 394 $[MH]^+$.

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline (27). 3-Chloro-2,4-difluoroaniline (1.7 g, 10.1 mmol) and 5N hydrogen chloride in isopropanol (2 mL) were added to a suspension of **26** (4 g, 10.1 mmol) in isopropanol (50 mL). The mixture was stirred at 80°C for 3 h. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 5-10% 7N methanolic ammonia in dichloromethane) to give 3.63 g of **27** (85%). ^{1}H NMR (DMSO-d_6 + CD_3CO_2D): δ 2.15 (m, 2H), 2.30 (m, 2H), 3.34 (m, 2H), 3.47 (m, 2H), 4.01 (s, 3H), 4.91 (m, 1H), 7.03 (m, 1H), 7.58 (m, 2H), 7.90 (s, 1H), 8.55 (s, 1H). MS-ESI *m/z* 421 $[MH]^+$.

4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline (28). 3-Chloro-4-fluoroaniline (1.14 g, 7.8 mmol) and 5N hydrogen chloride in isopropanol (80 μL) were added to a suspension of **26** (3.08 g, 7.8 mmol) in isopropanol (50 mL). The mixture was stirred at 80°C for 1 h. After cooling, the solid was filtered, washed with cold isopropanol and diethyl ether to give 3.95 g of 6-[(1-*tert*-butoxycarbonylpiperidin-4-yl)oxy]-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline. This compound (3.95 g) was stirred in a mixture of dichloromethane (15 mL) – TFA (15 mL). The mixture was stirred at room temperature for 1 h. After evaporation of the solvents, the residue was diluted with dichloromethane and washed with aqueous ammonia. The organic layer was dried over magnesium sulfate and the solvents evaporated to give 2.44 g of **28** (76%). ^{1}H NMR (DMSO-d_6): δ 1.52 (m, 2H), 1.98 (m, 2H), 2.61 (m, 2H), 3.00 (m, 2H), 3.94 (s, 3H), 4.62 (m, 1H), 7.22 (s, 1H), 7.45 (m, 2H), 7.77 (m, 1H), 7.86 (s, 1H), 8.11 (m, 1H), 8.49 (s, 1H), 9.52 (br s, 1H). MS-ESI *m/z* 403 $[MH]^+$.

A similar procedure was used to prepare **29, 30.**

4-(5-Chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline (29). 2.62 g, 85%. ^{1}H NMR (DMSO-d_6 + CF_3CO_2D): δ 2.02 (m, 2H), 2.24 (m, 2H), 3.18 (m, 2H), 3.32 (m, 2H), 4.05 (s, 3H), 4.85 (m, 1H), 7.40 (s, 1H), 7.55 (m, 2H), 7.74 (m, 1H), 8.15 (s, 1H), 8.94 (s, 1H). MS-ESI *m/z* 403 $[MH]^+$.

4-(3-Chloroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline (30). 3.14 g, 80%. ^{1}H NMR (DMSO-d_6 + CF_3CO_2D): δ 1.98 (m, 2H), 2.26 (m, 2H), 3.21 (m, 2H), 3.32 (m, 2H), 4.05 (s, 3H), 4.99 (m, 1H), 7.41 (m, 2H), 7.54 (m, 1H), 7.73 (d, 1H), 7.91 (s, 1H), 8.48 (s, 1H), 8.96 (s, 1H). MS-ESI *m/z* 385 $[MH]^+$.

Using a similar method, **35** was obtained from **32** and 3-chloro-2-fluoroaniline

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-(pyrrolidin-3-yloxy)quinazoline (35). 920 mg, 24% from **25** (2 steps). ^{1}H NMR ($CDCl_3$): δ 2.30-2.10 (m, 2H), 3.03 (m, 1H), 3.13 (m, 1H), 3.31 (m, 1H), 3.38 (m, 1H), 4.00 (s, 3H), 5.03 (m, 1H), 7.15 (m, 2H), 7.21 (m, 1H), 7.28 (s, 1H), 7.50 (br s, 1H), 8.41 (m, 1H), 8.69 (s, 1H). MS-ESI *m/z* 389 $[MH]^+$.

3-Chloro-2-fluoroaniline (2.54 mmol) and 4N hydrogen chloride in dioxane (2.5 mL) were added to the corresponding chloroquinazoline (2.54 mmol) in acetonitrile (20 mL). The mixture was refluxed for 4 h. After cooling, 7N methanolic ammonia (5 mL) and dichloromethane (50 mL) were added. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 5-10% 7N methanolic ammonia in dichloromethane) to give **34** and **36**.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-(piperidin-3-yloxy)quinazoline (34). 1.09 g, 53% from **31**. ^{1}H NMR ($CDCl_3$): δ 1.58 (m, 1H), 1.90 (m, 2H), 2.13 (m, 1H), 2.77 (m, 1H), 2.92 (m, 2H), 3.30 (m, 1H), 4.01 (s, 3H), 4.45 (m, 1H), 7.16 (m, 3H), 7.28 (m, 2H), 8.37 (m, 1H), 8.68 (s, 1H). MS-ESI *m/z* 403 $[MH]^+$.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-[2-(*N*-methylamino)ethoxy]quinazoline (36). 1.3 g, 86% from **33**. ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 3.3 (m, 2H), 3.96 (s, 3H), 4.39 (m, 2H), 7.25 (m, 2H), 7.50 (m, 2H), 7.98 (m, 1H), 8.40 (s, 1H), 9.85 (br s, 1H). MS-ESI *m/z* 377 $[MH]^+$.

6-{[(1-*tert*-Butoxycarbonyl)azetidin-3-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (37). DTAD (2.3 g, 10 mmol) was added portionwise to triphenylphosphine (2.62 g, 10 mmol) in THF (40 mL) cooled at –20°C. The mixture was stirred for 15 min at –20°C. 1-*tert*-Butoxycarbonyl-4-hydroxyazetidine (219 mg, 1.26 mmol) [prepared as described in Falgueyret, J.P., *J. Med. Chem*, **2001**, *44*, 94] in THF (10 mL) was added dropwise and the mixture was stirred for 15 min at –20°C. 4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline **18** (1.59 g, 5 mmol) was added and the mixture was heated to 70°C for 24 h. After cooling, the solvents were evaporated under vacuum and the residue was purified by chromatography on silica gel (eluant: 40% to 60% ethyl acetate in dichloromethane) to give 2.0 g of **37** (84%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 4.04 (s, 3H), 4.16 (m, 2H), 4.39 (m, 2H), 5.06 (m, 1H), 6.83 (s, 1H), 7.15 (m, 2H), 7.32 (s, 1H), 7.4 (br s, 1H), 8.42 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* 475 $[MH]^+$.

The deprotection step for making **28** was repeated on **37** to give **38.**

6-(Azetidin-3-yloxy)-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (38). 1.1 g, 74%. ^{1}H NMR (DMSO-d_6 + CF_3CO_2D): δ 4.08 (s, 3H), 4.18 (m, 2H), 4.63 (m, 2H), 5.26 (m, 1H), 7.44 (m, 2H), 7.58 (m, 1H), 7.70 (m, 2H), 8.95 (s, 1H). MS-ESI *m/z* 375 $[MH]^+$.

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (8). 2-Chloro-N-methylacetamide (51 mg, 0.47 mmol) was added dropwise to a mixture of **27** (200 mg, 0.47 mmol), potassium iodide (79 mg, 0.47 mmol) and potassium carbonate (79 mg, 0.57 mmol) in dimethylacetamide (5 mL). The mixture was heated at 70°C for 1 h. After cooling and filtration of the solids, the filtrate was purified by preparative HPLC eluting with a mixture of water and acetonitrile containing 2 g/L of ammonium formate (gradient) to give 55 mg of **8** (24%). ^{1}H NMR ($CDCl_3$): δ 1.98 (m, 2H), 2.07 (m, 2H), 2.44 (m, 2H), 2.86 (m, 2H), 2.87 (d, 3H), 3.06 (s, 2H), 4.01 (s, 3H), 4.48 (m, 1H), 7.07 (m, 1H), 7.15 (m, 1H), 7.20 (s, 1H), 7.30 (m, 2H), 8.32 (m, 1H), 8.66 (s, 1H). MS-ESI *m/z* 492 $[MH]^+$. Anal. ($C_{22}H_{23}ClFN_5O_3 \cdot 0.05\ H_2O \cdot 1.03\ CH_3CN$) C, H, N. Found C, 56.47; H, 5.19; N, 15.98; Requires C, 56.25; H, 5.12; N, 15.78%.

A similar procedure was used to prepare **7, 9, 10, 12-15**.

4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (7). 140 mg, 60% from **28**. ^{1}H NMR ($CDCl_3$): δ 1.91 (m, 2H), 2.03 (m, 2H), 2.37 (m, 2H), 2.80 (m, 2H), 2.85 (d, 3H), 3.02 (s, 2H), 3.98 (s, 3H), 4.42 (m, 1H), 7.16 (m, 2H), 7.34 (s, 1H), 7.55 (m, 1H), 7.72 (s, 1H), 7.83 (m, 1H), 8.65 (s, 1H). MS-ESI *m/z* 474 $[MH]^+$. Anal. ($C_{23}H_{25}ClFN_5O_3 \cdot 0.3\ H_2O$) C, H, N. Found C, 58.02; H, 5.27; N, 14.24; Requires C, 57.63; H, 5.38; N, 14.61%.

4-(5-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (10). 140 mg, 60% from **29**. ^{1}H NMR ($CDCl_3$): δ 1.97 (m, 2H), 2.07 (m, 2H), 2.45 (m, 2H), 2.85 (m, 2H), 2.87 (d, 3H), 3.06 (s, 2H), 4.02 (s, 3H), 4.48 (m, 1H), 7.18-7.03 (m, 4H), 7.31 (s, 1H), 7.35 (br s, 1H), 8.73 (m, 2H). MS-ESI *m/z* 474 $[MH]^+$. Anal. ($C_{23}H_{25}ClFN_5O_3 \cdot 0.5\ H_2O$) C, H, N. Found C, 57.02; H, 5.23; N, 14.38; Requires C, 57.20; H, 5.43; N, 14.50%.

4-(3-Chloroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (9). 150 mg, 63% from **30**. ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 2H), 2.02 (m, 2H), 2.35 (m, 2H), 2.79 (m, 2H), 2.84 (d, 3H), 3.01 (s, 2H), 3.97 (s, 3H), 4.42 (m, 1H), 7.16-7.10 (m, 2H), 7.30 (m, 1H), 7.39 (s, 1H), 7.59 (d, 1H), 7.79 (s, 1H), 7.89 (br s, 1H), 8.68 (s, 1H). MS-ESI *m/z* 456 $[MH]^+$. Anal. ($C_{23}H_{26}ClN_5O_3 \cdot 2.7\ H_2O$) C, H, N. Found C, 54.51; H, 5.91; N, 13.84; Requires C, 54.75; H, 6.27; N, 13.88%.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-3-yl]oxy}quinazoline (12). 200 mg, 68% from **34**. ^{1}H NMR ($CDCl_3$): δ 1.54 (m, 1H), 2.00-1.75 (m, 3H), 2.44 (m, 1H), 2.54 (m, 1H), 2.62 (m, 1H), 2.70 (d, 3H), 2.78 (m, 1H), 2.95 (d, 1H), 3.01 (d, 1H), 3.93 (s, 3H), 4.47 (m, 1H), 7.08 (m, 3H), 7.24 (br s, 2H), 7.70 (s br, 1H), 8.19 (m, 1H), 8.60 (s, 1H). MS-ESI *m/z* 474 $[MH]^+$. Anal. ($C_{23}H_{25}ClFN_5O_3 \cdot 1.15\ H_2O$) C, H, N. Found C, 55.48; H, 5.16; N, 13.94; Requires C, 55.85; H, 5.56; N, 14.16%

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)pyrrolidin-3-yl]oxy}quinazoline (13). 122 mg, 69% from **35**. ^{1}H NMR ($CDCl_3$): δ 2.07 (m, 2H), 2.31 (m, 1H), 2.52 (m, 1H), 2.75 (d, 3H), 2.86 (m, 1H), 2.92 (m, 1H), 2.97 (m, 1H), 3.08 (d, 1H), 3.14 (d, 1H), 3.91 (s, 3H), 4.90 (m, 1H), 7.08 (m, 3H), 7.20 (s, 1H), 7.77 (s br, 1H), 8.20 (m, 1H), 8.60 (s, 1H). MS-ESI *m/z* 460 $[MH]^+$. LC t_R: 1.69 min.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{2-[*N*-(*N'*-methylcarbamoylmethyl)-*N*-methylamino]ethoxy}quinazoline (15). 139 mg, 62% from **36**. ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 2.84 (d, 3H), 2.97 (t, 2H), 3.21 (s, 2H), 4.04 (s, 3H), 4.22 (t, 2H), 7.10 (s, 1H), 7.16 (m, 2H), 7.31 (s, 1H), 7.42 (br s, 1H), 7.48 (br s, 1H), 8.45 (m, 1H), 8.71 (s, 1H). MS-ESI *m/z* 448 $[MH]^+$. Anal. ($C_{21}H_{23}ClFN_5O_3 \cdot 1.2\ H_2O$) C, H, N. Found C, 53.61; H, 5.32; N, Requires C, 53.72; H, 5.45; N, 14.92%.

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)azetidin-3-yl]oxy}quinazoline (14). 110 mg, 49%. ^{1}H NMR ($CDCl_3$): δ 2.87 (d, 3H), 3.30 (s, 2H), 3.52 (m, 2H), 4.01 (m, 2H), 4.04 (s, 3H), 4.97 (m, 1H), 6.83 (s, 1H), 6.97 (br s, 1H), 7.16 (m, 2H), 7.32 (s, 1H), 7.35 (br s, 1H), 8.49 (m, 1H), 8.72 (s, 1H). MS-ESI *m/z* 446 $[MH]^+$. Anal. ($C_{21}H_{21}ClFN_5O_3 \cdot 0.8\ H_2O$) C, H, N. Found C, 54.41; H, 4.80; N, 14.99; Requires C, 54.80; H, 4.95; N, 15.21%;

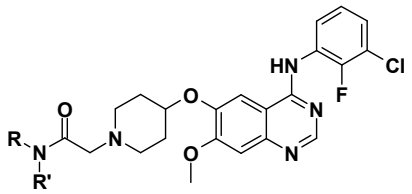
Mouse, Rat and dog pharmacokinetics

Pharmacokinetics were determined in the rat and dog following single intravenous or oral administrations of the compound. For the i.v. and p.o. studies, the compounds (as free base) were formulated in a mixture of hydroxypropyl-β-cyclodextrin/DMSO/Sorrenson's phosphate buffer (pH 5.5). Some blood was then collected into tubes containing anticoagulant (EDTA) at different timepoints. Plasma samples were obtained by centrifugation and transferred into separate neutral polypropylene tubes and stored frozen at or below -20 °C. Plasma samples after solid-phase extraction were analysed by high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS-MS). Pharmacokinetic analysis of the plasma concentration data was performed using the pharmacokinetic data analysis program WinNonLin Professional (Pharsight Corporation).
High dose oral nude mouse pharmacokinetics were determined with **1**, **2** and **7** with the following formulation: suspension of free base in a 1% (v/v) solution of polyoxyethylenesorbitan monooleate (Tween 80) in de-ionized water.

Biological evaluation.

Detailed protocols for all in vitro and in vivo biological assays (isolated kinase assays, kinase selectivity, in vitro EGFR, HER2 and HER3 phosphorylation assays, in vivo tumour growth inhibition experiments) can be found in Ref 16.
Confidence interval ratios (95% confidence interval, CIR) are quoted for the tables below

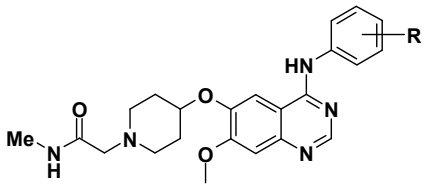
Table 1. Enzyme and cell data for compounds **1-6**



	NRR'	HER2 enz. IC_{50}	CIR Enz.	cl.24 IC_{50} (p-HER2)	CIR cl.24
1	NH_2	0.046	2.54	0.107	2.75
2	NHMe	0.014	2.07	0.060	1.29
3	NHEt	0.033	7.8	0.27	NC[a]
4	NHCH2CH2OMe	0.091	3.9	0.25	4.3
5	NH^iPr	0.11	3.6	0.41	NC[a]
6	NMe_2	0.22	2.76	0.67	NC[a]

IC_{50} unit: μM; a) NC: not calculated given the number of experiments (n=2)

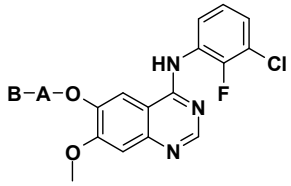
Table 2. Cell data for compounds **7-10**



	R	cl.24 IC_{50} (p-HER2)	CIR cl.24
7	3-Cl 4-F	0.26	2.72
8	2-F 3-Cl 4-F	0.089	2.52
9	3-Cl	0.36	NC[a]
10	2-F 5-Cl	0.86	NC[a]

IC_{50} unit: μM; a) NC: not calculated given the number of experiments (n=2)

Table 3. Cell data for compounds **11-15**



	A	B	cl.24 IC_{50} (p-HER2)	CIR cl.24
11	4-piperidine	$CH_2CH_2CONHMe$	0.55	NC[a]
12	3-piperidine	$CH_2CONHMe$	0.23	NC[a]
13	3-pyrrolidine	$CH_2CONHMe$	0.25	4.4
14	3-azetidine	$CH_2CONHMe$	1.1	NC[a]
15	-$CH_2CH_2N(Me)$-	$CH_2CONHMe$	1.5	NC[a]

IC_{50} unit: μM; a) NC: not calculated given the low number of experiments (n=2)

X-ray structure determination of compound 2

Suitable single crystals were obtained from aqueous acetonitrile. Crystals were colourless, prismatic rods. A data set was collected at room temperature. Experimental details of the investigation are enclosed in Table S1. The final R-value is 4.5%. The substance crystallises from aqueous Acetonitrile in a centrosymmetric orthorhombic space group Pbca with eight molecules in the unit cell. The substance crystallized as a dihydrate acetonitrile solvate.

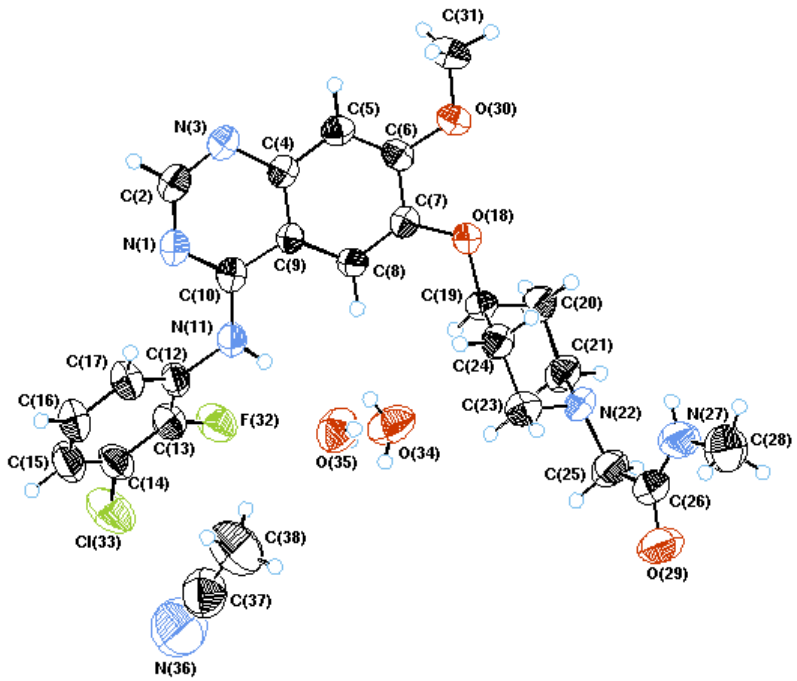


Figure 1. The molecular conformation of **2** Dihydrate Acetonitrile solvate is shown with the thermal displacement ellipsoids drawn at 50% probability and hydrogen atoms as spheres of arbitrary radius. The crystallographic numbering of the atoms is also shown.

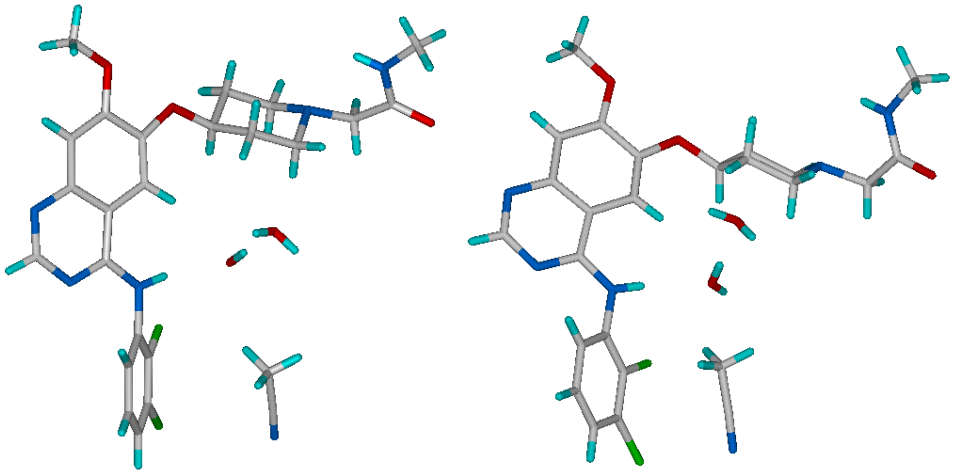


Figure 2. The molecular conformation of **2** Dihydrate Acetonitrile solvate is shown from different views.

Table S1 Experimental Data and Selected Details of the Refinement Calculations

Crystal data	
$C_{23}H_{25}Cl_1F_1O_3N_5 * 2H_2O * CH_3CN$	
Mw = 473.93 + 41.05 + 2(18.02)	MoK (α) radiation: λ = 0.71073 Å
Crystal system: Orthorhombic	Space group: Pbca
Unit-cell parameters:	average values from 21882 image indexed reflections
a = 6.751(1) Å	α = 90°
b = 25.655(1) Å	β = 90°
c = 31.798(1) Å	γ = 90°
V = 5507.3(1) $Å^3$	crystal shape: rod
Z = 8	0.25 x 0.08 x 0.05 mm
Dc = 1.3291(1) Mg m^{-3}	colourless
T = room temp	μ = 0.19 mm^{-1}
F(000) = 2320 electrons	
Data collection	
BrukerNonius KappaCCD Diffractometer	
hkl-range:	$0 < h < 8$, $0 < k < 33$, $0 < l < 41$
Number of collected frames:	273
Distance: crystal-detector	Dx = 38.1 mm
Phi-rotation step (°)	1.0
Exposure time (s):	30
Resolution (high, low):	0.62, 2.82 Å
Covered θ-range:	1.02 – 27.5°
Total number of measured reflections:	5896
Number of unique observed reflections, $F^2 > 2\sigma(F^2)$:	1982
Absorption correction:	none
Refinement	
SHELXL-97	$(\Delta/\sigma)_{max}$ = 0.001
Refinement on F^2	$(\Delta/\sigma)_{mean}$ = 0.000
R = 0.0446	$\Delta\rho_{max}$ = 0.16 $eÅ^{-3}$
Rw (on F^2) = 0.1113	$\Delta\rho_{min}$ = -0.25 $eÅ^{-3}$
Weighting scheme:	$w = 1/[\sigma^2(F_o^2) + (0.0525P)^2 + 0.0000P]$; $P = (F_o^2 + 2F_c^2)/3$
Atomic scattering factors:	SHELXL-97 (1997, ver 2.0)
1982 observations	
343 parameters	
Atomic displacement parameters:	
non-H atoms	anisotropic
H-atoms	isotropic, $U_{(iso)}$ = ride on parent atom + 0.005 $Å^2$
Goodness-of-fit	0.743
Packing coefficient (%filled space)	66.8

Data collection: KappaCCD Server Software (Nonius BV, 2000). Cell refinement: Denzo-SMN Software Package (Otwinowski & Minor, 1997). Data reduction: MaXus Software Package (MacKay et al., 2000): Programs used to solve and refine the structure: SIR97, SHELXL-97-program. Molecular graphics: *ORTEPII, XXmol, PLUTON* (Spek, 2003). Software used to prepare material for publication: CIF and PLATON (Spek, 1996, 2003).