General Procedures.

All preparations were carried out under an inert atmosphere and at room temperature unless otherwise stated. Flash chromatography was carried out on Merck Kieselgel 60 (Art. 9385). The purities of compounds for test were assessed by analytical HPLC on a Hichrom S5ODS1 Sperisorb Column System set to run isocratically with 60-70% MeOH + 0.2% CF_3COOH in H_2O as eluent. TLCs were performed on precoated silica gel plates (Merck Art. 5715), and the resulting chromatograms were visualised under UV light at 254 nm. Melting points were determined on a Kofler Block or with a Büchi melting point apparatus on compounds isolated as described in the experimental procedures and are uncorrected. NMR spectra were determined in Me_2SO-d_6 solution (unless otherwise stated) on a Bruker AM 200 (200MHz) spectrometer or on a Jeol JNM EX 400 (400MHz). For ^{13}C NMR spectra, ring carbon atoms have been numbered as shown below.

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. Fast atom bombardment (FAB) mass spectra were determined with VG MS9 spectrometer and Finnigan Incos data system, using Me_2SO as solvent and glycerol as matrix or with a Finnigan SSQ 7000 for the electro-spray technique. With the appropriate mode either positive or negative ion data could be collected. NMR and mass spectra were run on isolated intermediates and final products and are consistent with the proposed structures. For microanalysis, all adducts mentioned were measured : water was measured by the Karl-fisher method using a Mettler DL 18; HCl content was determined by titration using silver nitrate solution and a Metrohm 686 and organic adducts were measured by ^1H NMR.

Of the anilines used, 2-fluoro-4-chloro, 2-fluoro-4-bromo, 2-fluoro-4-methyl, 2,6-difluoro-4-bromo, 2,6-difluoro-4-chloro were commercially available and 2-fluoro-4-cyano,; 2-fluoro-4-chloro-5-hydroxy and 2-fluoro-4-methyl-5-hydroxy were prepared as already described.[18] 4-hydroxy-1-methylpiperidine; 2-hydroxyethy-1-morpholine were commercially available.

The following abbreviations have been used : DMF : N,N-dimethylformamide; DEAD : diethylazodicarboxylate; ADDP : 1,1'-(azodicarbonyl)dipiperidine; TFA: trifluoroacetic acid; DMSO: dimethylsulfoxide.

***N*-(4-Bromo-2-fluorophenyl)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-amine 5 (Procedure B).** A solution of *N*-(4-Bromo-2-fluorophenyl)-7-(3-chloropropoxy)-6-methoxyquinazolin-4-amine **67** (0.15 g, 0.34 mmol) in N-methylpiperazine (2 mL) was heated at 100^{0}C for 2 h. After cooling, the mixture was poured onto an aqueous solution of 10% sodium carbonate (15 mL) and diluted with ethylacetate (20 mL). The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered, washed with ether (2 mL) and dried under vacuum. The solid was dissolved in methylene chloride (1 mL) and 3.8 M hydrogen chloride in ether (0.5 mL) was added. The solid was filtered, washed with ether (1 mL) and dried under vacuum to give 95 mg of **5** (45%). ^{1}H NMR: ($DMSOd_6$; CF_3COOD) δ 2.28 (m, 2H), 2.95 (s, 3H), 3.45 (t, 2H), 3.5-3.7 (m, 8H), 4.03 (s, 3H), 4.35 (t, 2H), 7.4 (s, 1H), 7.55 (d, 1H), 7.6 (s, 1H), 7.75 (d, 1H), 8.11 (s, 1H), 8.85 (s, 1H). MS-ESI *m/z* 504-506 $[MH]^+$. Anal. ($C_{23}H_{27}N_5O_2BrF$ 1 H_2O, 2.6 HCl) C, H, N.

***N*-(4-Cyano-2-fluorophenyl)-6-methoxy-7-{[(2*E*)-4-pyrrolidin-1-ylbut-2-enyl]oxy}quinazolin-4-amine 12 (Procedure E).** Diethyl azodicarboxylate (0.25 mL, 1.5 mmol) was added dropwise to a stirred mixture of (E)-4-pyrrolidin-1-ylbut-2-en-1-ol **68** (0.2 g, 1.4 mmol), *N*-(4-cyano-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **42** (0.155 g, 0.5 mmol) and triphenylphosphine (0.4 g, 1.5 mmol) in methylene chloride (1 mL). The reaction mixture was stirred for 2 h at ambient temperature. The volatiles were removed by evaporation and the residue was purified by column chromatography eluting with methylene chloride / ethyl acetate / methanol 90/5/5 followed by 80/10/10. The purified product was dissolved in methylene chloride / methanol (5 mL / 5 mL) and 3.5 M hydrogen chloride in diethylether (0.5 mL) was added. The precipitated product was collected by filtration, washed with diethylether and dried under vacuum to give 45 mg of **12**

hydrochloride (18%). ^{1}H NMR (DMSOd_6, CF_3COOD): δ 1.8-1.92 (m, 2H), 2.0-2.1 (m, 2H), 3.0-3.1 (m, 2H), 3.42-3.52 (m, 2H), 3.9 (d, 2H), 4.02 (s, 3H), 4.9 (d, 2H), 6.02 (td, 1H), 6.3 (td, 1H), 7.4 (s, 1H), 7.8-7.9 (m, 2H), 8.12 (d, 1H), 8.15 (s, 1H), 8.95 (s, 1H). MS-ESI *m/z* 434 $[MH]^+$

***N*-(4-Chloro-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine 15.** 3.5 M Hydrogen chloride in ethanol (75 µL, 0.26 mmol) was added to a suspension of 4-chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazoline **64** (80 mg, 0.25 mmol), in isopropanol (3 mL), the mixture was heated to 50°C and 4-chloro-2-fluoroaniline (44 mg, 0.3 mmol) was added. The mixture was refluxed for 30 min. After cooling, the mixture was diluted with diethylether (3 mL). The precipitate was filtered, washed with diethylether (2 mL) and dried under vacuum to give 105 mg of **15** hydrochloride (82%). The NMR spectrum of the protonated form of **15** hydrochloride shows the presence of two forms A and B in a ratio A:B of approximately 9:1. ^{1}H NMR (DMSOd_6; CF_3COOD): δ 1.55-1.7 (m, form A 2H), 1.85-2.0 (m, form B 4H), 2.05 (d, form A 2H), 2.1-2.2 (m, form A 1H), 2.35 (s, 3H); 2.79 (s, form A 3H), 2.82 (s, form B 3H), 3.03 (t, form A 2H), 3.2-3.3 (m, form B 2H); 3.3-3.4 (m, form B 2H), 3.52 (d, form A 2H), 4.02 (s, 3H), 4.13 (d, form A 2H), 4.3 (d, form B 2H), 7.41 (s, 1H), 7.47 (dd, 1H), 7.63 (t, 1H), 7.69 (dd, 1H), 8.19 (s, 1H), 8.88 (s, 1H). MS - ESI *m/z* 431-433 $[MH]^+$. Anal. ($C_{22}H_{24}N_4O_2ClF$ 0.4 H_2O, 2 HCl) C, H, N.

2-Chloro-4-fluoro-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)phenol 17. A solution of 4-chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazoline **64** (136 mg, 0.42 mmol) and 4-chloro-2-fluoro-5-hydroxyaniline[18] (82 mg, 0.51 mmol) in isopropanol (5 mL) containing 5.5 M hydrogen chloride in isopropanol (85 µL) was heated at 80 ^{0}C for 1.5 h. The solid was filtered, washed with isopropanol (2 mL) followed by diethylether (2 mL) and dried under vacuum. The solid was recristallised from isopropanol / methylene chloride to give 200 mg of **17** (90%). ^{1}H NMR: δ 1.55-1.7 (m, 2H), 2.02 (d, 2H), 2.1-2.2 (m, 1H), 2.75 (2s, 3H), 2.95-3.1 (m, 2H), 3.4-3.5 (m,

2H), 4.0 (s, 3H), 4.1 (d, 2H), 7.15 (d, 1H), 7.35 (s, 1H), 7.51 (d, 1H), 8.18 (s, 1H), 8.75 (s, 1H). MS-ESI *m/z* 447-449 $[MH]^+$. Anal. ($C_{22}H_{24}N_4O_3ClF$ 2.0 HCl, 0.5 C_3H_8O, 0.8 H_2O) C, H, N.

2-Methyl-4-fluoro-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)phenol hydrochloride 18. A solution of 4-chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazoline **64** (136 mg, 0.42 mmol) and 2-fluoro-5-hydroxy-4-methylaniline[18] (71.5 mg, 0.51 mmol) in isopropanol (5 mL) containing 5.5 M hydrogen chloride in isopropanol (85 µL) was heated at 80 ^{0}C for 1.5 h. The solid was filtered, washed with isopropanol (2 mL) followed by diethylether (2 mL) and dried under vacuum. The solid was recristallised from isopropanol / methylene chloride to give 135 mg of **18** hydrochloride (75%) ^{1}H NMR: δ 1.6-1.7 (m, 2H), 2.0 (d, 2H), 2.1-2.2 (m, 1H), 2.03 (s, 3H), 2.75 (2s, 3H), 2.95-3.1 (m, 2H), 3.4-3.5 (m, 2H), 4.0 (s, 3H), 4.1 (d, 2H), 6.9 (d, 1H), 7.1 (d, 1H), 7.4 (s, 1H), 8.2 (s, 1H), 8.75 (s, 1H), 9.7 (s, 1H). MS-ESI *m/z* 427 $[MH]^+$. Anal. ($C_{23}H_{27}N_4O_3F$ 1.95 HCl, 0.65 C_3H_8O, 1.0 H_2O) C, H, N.

***N*-(4-Bromo-2,4-difluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine 20 (Procedure H).** Under argon, sodium hydride (60%, 372 mg, 9.3 mmol) was added to a solution of 4-bromo-2,6-difluoroaniline (1.67 g, 8.08 mmol) in DMF (50 mL). After stirring for 30 min at ambient temperature, 4-chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazoline **64** (1.3 g, 4.04 mmol) was added and stirring was continued for a further 20 h. The mixture was poured onto water (130 mL) and extracted with ethyl acetate (100 mL). The organic layers were washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography on silica, eluting with methylene chloride / methanol (95/5) followed by methylene chloride / methanol containing ammonia (1%) (90/10). The fractions containing the expected product were combined and evaporated. The residue was triturated with diethylether (10 mL), collected by filtration, washed with diethylether (5 mL) and dried under vacuum at 50 °C to give 1.4 g of **20** (70%). ^{1}H NMR: δ 1.3-1.45 (m, 2H), 1.8

(d, 2H), 1.7-1.9 (m, 1H), 1.9 (t, 2H), 2.17 (s, 3H), 2.8 (d, 2H), 3.95 (s, 3H), 4.02 (d, 2H), 7.2 (s, 1H), 7.63 (s, 1H), 7.6 (s, 1H), 7.82 (s, 1H), 8.35 (s, 1H). MS-ESI *m/z* 493-495 $[MH]^+$. Anal. ($C_{22}H_{23}N_4O_2BrF_2$) C, H, N.

***N*-(4-Methyl-2-fluorophenyl)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-amine 23 (Procedure J).** A suspension of *tert*-butyl 4-[({4-[(2-fluoro-4-methylphenyl)amino]-6-methoxyquinazolin-7-yl}oxy)methyl]piperidine-1-carboxylate **47** (318 mg, 0.64 mmol) in methylene chloride (5 mL) containing TFA (2.5 mL) was stirred at ambient temperature for 2 h. The volatiles were removed under vacuum and the residue was partitioned between methylene chloride (5 mL) and water (5 mL). The aqueous layer was adjusted to pH 10-11 with aqueous sodium bicarbonate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation to give 220 mg of **23** (87%). ^1H NMR: δ 1.15-1.3 (m, 2H), 1.75 (d, 2H), 1.85-2.0 (m, 1H), 2.4 (s, 3H), 3.0 (d, 2H), 3.3-3.4 (d, 2H), 3.95 (s, 3H), 4.0 (d, 2H), 7.04 (d, 1H), 7.15 (d, 1H), 7.17 (s, 1H), 7.4 (t, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H). MS-ESI *m/z* 397 [MH]+

***N*-(4-Chloro-2,6-difluorophenyl)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-amine 24 (Procedure J).** A solution of *tert*-butyl 4-[({4-[(4-chloro-2,6-difluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)methyl]piperidine-1-carboxylate **49** (95 mg, 0.2 mmol) in methylene chloride (2 mL) containing TFA (800 μL) was stirred at ambient temperature for 2 h. The volatiles were removed under vacuum and the residue was suspended in water. The aqueous layer was adjusted to pH 10 and was extracted with methylene chloride (10 mL). The organic layer was washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was triturated with diethylether (2 mL) and dried under vacuum to give 20 mg of **24** (26%). ^1H NMR: δ 1.2-1.3 (m, 2H); 1.75 (d, 2H) ; 1.85-2.0 (br s, 1H) ; 2.5 (d, 2H) ; 3.0 (d, 2H) ; 3.97 (s, 3H) ; 4.0 (d, 2H) ; 7.2 (s, 1H); 752 (d, 2H) ; 7.85 (s, 1H) ; 8.35 (s, 1H). MS-ESI *m/z* 435-437 $[MH]^+$

***N*-(4-Bromo-2,6-difluorophenyl)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-amine 25 (Procedure J).** A solution of *tert*-butyl 4-[({4-[(4-bromo-2,6-

difluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)methyl]piperidine-1-carboxylate **48** (578 mg, 1 mmol) in methylene chloride (10 mL) containing TFA (4 mL) was stirred at ambient temperature for 2 h. The volatiles were removed under vacuum and the residue was suspended in water. The aqueous layer was adjusted to approximately pH 10 and was extracted with methylene chloride (10 mL). The organic layer was washed with water, brine , dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was triturated with diethylether (2 mL) and dried under vacuum to give 110 mg of **25** (23%). ^{1}H NMR: δ 1.15-1.3 (m, 2H), 1.75 (d, 2H), 1.85-2.0 (br s, 1H), 2.5 (d, 2H), 3.0 (d, 2H), 3.97 (s, 3H), 4.0 (d, 2H), 7.2 (s, 1H), 7.62 (d, 2H), 7.82 (s, 1H), 8.35 (s, 1H). MS-ESI *m/z* 479-481 $[MH]^+$. ^{1}H NMR ($DMSOd_6$; CF_3COOD) : δ 1.5-1.65 (m, 2H), 2.0 (d, 2H), 2.15-2.3 (br s, 1H), 3.0 (t, 2H), 3.4 (d, 2H), 4.02 (s, 3H), 4.15 (d, 2H), 7.4 (s, 1H), 7.75 (d, 2H), 8.1 (s, 1H), 8.92 (s, 1H).

***N*-(4-Chloro-2-fluorophenyl)-6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinazolin-4-amine 26.** A suspension of 4-chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)ethoxy]quinazoline **65** (150 mg, 0.45 mmol) and 4-chloro-2-fluoroaniline (60μL, 0.53 mmol) in isopropanol (2 mL) containing 6 M hydrogen chloride in isopropanol (84 μL, 0.5 mmol) was heated at 80 ^{0}C for 1 h. After cooling, diethylether was added and the solid was filtered, washed with isopropanol (2 mL) followed by diethylether (2 mL) and dried under vacuum to give 180 mg of **26** hydrochloride (77%). ^{1}H NMR ($DMSOd_6$, CF_3COOD): δ 1.4-1.55 (m, 2H), 1.7-1.9 (m, 3H), 2.0 (d, 2H), 2.8 (s, 3H), 3.0 (t, 2H), 3.45 (d, 2H), 4.02 (s, 3H), 4.3 (t, 2H), 7.4 (s, 1H), 7.5 (d, 1H), 7.62 (dd, 1H), 7.68 (d, 1H), 8.15 (s, 1H), 8.9 (s, 1H). MS-ESI *m/z* 445-447 $[MH]^+$.

***N*-(4-Chloro-2-fluorophenyl)-6-methoxy-7-{[(3*R*)-1-methylpiperidin-3-yl]methoxy}quinazolin-4-amine 29 (Procedure E).** A solution of (R)-1-methylpiperidin-3-ylmethanol **50** (2.29 g, 18 mmol) in methylene chloride (10 mL) was added to a stirred mixture of *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **39**[18] (4.0 g, 12.5 mmol), and triphenylphosphine (9.81 g, 37.5 mmol) in methylene chloride (200 mL). Diethyl azodicarboxylate (5.87 mL, 37 mmol) was added dropwise and the reaction mixture

was stirred for 18 h at ambient temperature. The volatiles were removed by evaporation and the residue was purified by column chromatography eluting with methylene chloride / methanol / aqueous ammonia (a gradient from 100/0/0 to 85/15/0.1). The purified product was triturated with ethyl acetate, collected by filtration, washed with ethyl acetate and dried to give 2.78 g of **29** (52%). ^{1}H NMR: δ 1.08 (m, 1H), 1.50 (m, 1H), 1.64 (m, 1H), 1.80 (m, 3H), 2.07 (m, 1H), 2.16 (s, 3H), 2.62 (d, 1H), 2.81 (d, 1H), 3.92 (s, 3H), 4.02 (d, 2H), 7.18 (s, 1H), 7.32 (d, 1H), 7.55 (m, 2H), 7.79 (s, 1H), 8.34 (s, 1H), 9.50 (s, 1H). MS - ESI *m/z* 431 $[MH]^+$. Anal. ($C_{22}H_{24}N_4O_2ClF$) H, N; C: calc 61.3 found 60.7.

***N*-(4-Bromo-2-fluorophenyl)-6-methoxy-7-{[(3*R*)-1-methylpiperidin-3-yl]methoxy}quinazolin-4-amine 30 (Procedure E).** A mixture of *N*-(4-bromo-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **40** (224 mg, 0.6 mmol) and triphenylphosphine (0.48 g, 1.8 mmol) in methylene chloride (6 mL) was stirred at ambient temperature, under nitrogen, for 30 min. To this solution was added (R)-1-methyl-3-piperidinylmethanol **50** (0.16 g, 1.2 mmol) in methylene chloride (2 mL) followed by the slow addition of diethyl azodicarboxylate (0.32 g, 1.8 mmol). The mixture was then stirred for 4 h, the reaction diluted with diethylether (25 mL) and the resulting precipitate filtered off. The filtrate was concentrated under vacuum and the residue was purified by column chromatography, eluting with methylene chloride / methanol / aqueous ammonia (100/8/1). The fractions containing the expected product were combined and evaporated to dryness and the residue recristallised from acetonitrile to give 142mg of **30** (50 %). ^{1}H NMR: δ 1.16 (m, 1H), 1.50 (m, 1H), 1.62 (m, 1H), 1.80 (m, 2H), 1.90 (m, 1H), 2.08 (m, 1H), 2.15 (s, 3H), 2.60 (m, 1H), 2.81 (m, 1H), 3.91 (s, 3H), 4.00 (d, 2H), 7.14 (s, 1H), 7.48 (m, 2H), 7.62 (d, 1H), 7.77 (s, 1H), 8.30 (s, 1H), 9.49 (s, 1H). MS - ESI *m/z* 476 [MH]+. Anal. ($C_{22}H_{24}N_4O_2BrF$) C, H, N.

***N*-(4-Bromo-2-fluorophenyl)-6-methoxy-7-{[(3*S*)-1-methylpiperidin-3-yl]methoxy}quinazolin-4-amine 31 (Procedure E).** A mixture of *N*-(4-bromo-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **40**[18] (728 mg, 2.0 · mmol) and

triphenylphosphine (1.57 g, 6 mmol) in methylene chloride (20 mL) was stirred at ambient temperature, under nitrogen, for 30 min. To this solution was added (S)-1-methyl-3-piperidinylmethanol (0.52 g, 4 mmol) in methylene chloride (4 mL) followed by the slow addition of diethyl azodicarboxylate (0.94 mL, 6 mmol). The mixture was stirred for 1.5 h, diluted with diethylether (25 mL) and the resulting precipitate filtered off. The volatiles were removed under vacuum and the residue was purified by column chromatography, eluting with methylene chloride / methanol / aqueous ammonia (100/8/1). The fractions containing the expected product were combined and evaporated under vacuum. The solid was recristallised from acetonitrile to give 450 mg of **31** (47 %). ^{1}H NMR: δ 1.16 (m, 1H), 1.50 (m, 1H), 1.62 (m, 1H), 1.80 (m, 2H), 1.90 (m, 1H), 2.08 (m, 1H), 2.15 (s, 3H), 2.60 (m, 1H), 2.81 (m, 1H), 3.91 (s, 3H), 4.00 (d, 2H), 7.14 (s, 1H), 7.48 (m, 2H), 7.62 (d, 1H), 7.77 (s, 1H), 8.30 (s, 1H), 9.49 (s, 1H). MS-ESI *m/z* 476 [MH]+. Anal. ($C_{22}H_{24}N_4O_2BrF$) C, H, N.

***N*-7-Benzyloxy-(2-fluoro-4-methylphenyl)-6-methoxy-4-quinazolinylamine 35 (Procedure A).** A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride **32**[18] (1.55 g, 5.15 mmol) and 2-fluoro-4-methylaniline (700 mg, 5.67 mmol) in isopropanol (90 mL) containing 6.2 M hydrogen chloride in isopropanol (80 µL, 0.51 mmol) was stirred at 80 ^{0}C for 1.5 h. After cooling, the precipitate was collected by filtration, washed with isopropanol (1 mL), followed by diethylether (2 mL) and dried under vacuum to give 2 g of **35** hydrochloride (91%). ^{1}H NMR: δ 2.4 (s, 3H), 4.01 (s, 3H), 7.15 (d, 1H), 7.25 (d, 1H), 7.35-7.6 (m, 7H), 8.3 (s, 1H), 8.78 (s, 1H). MS-ESI *m/z* 390 [MH]$^+$. A sample of the free base was generated as described in procedure A for microanalysis. Anal. ($C_{23}H_{20}N_3O_2F$) C, H, N.

***N*-7-Benzyloxy-(4-cyano-2-fluorophenyl)-6-methoxy-4-quinazolinylamine 36 (Procedure G).** A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline **32**[18] (6.35 g , 21 mmol) and 4-cyano-2-fluoroaniline (3.45 g, 25 mmol) in isopropanol (150 mL) containing 3.8 M hydrogen chloride in isopropanol (2 mL) was refluxed for 2 h. After cooling, the precipitate was separated, washed with diethylether (4 mL) and dried under vacuum. The solid was dissolved in methylene chloride (50 mL) and the organic solution was washed with saturated

aqueous sodium bicarbonate. The organic layer was separated, washed with brine and dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethyl acetate / methylene chloride 1/1 followed by methylene chloride / ethyl acetate / methanol 50/45/5. The volatiles was removed under vacuum and the residue was dried under vacuum to give 4.65 g of **36** (55%). ^{1}H NMR ($DMSOd_6$, CF_3COOD): δ 4.03 (s, 3H), 5.4 (s, 2H), 7.35-7.6 (m, 6H), 8.8-8.9 (m, 2H), 8.1 (d, 1H), 8.13 (s, 1H), 8.93 (s, 1H). Anal. ($C_{23}H_{17}N_4O_2F$) C, H, N.

***N*-7-Benzyloxy-(4-chloro-2,6-difluorophenyl)-6-methoxy-4-quinazolinylamine 37 (Procedure H).** Under argon, sodium hydride (60%, 87 mg, 1.4 mmol) was added to a solution 4-chloro-2,6-difluoroaniline (200 mg, 1.22 mmol) in DMF (8 mL). After stirring 30 min at ambient temperature, 7-benzyloxy-4-chloro-6-methoxyquinazoline **32**[18] free base (184 mg, 0.61mmol) was added and stirring was continued for 20 h. The mixture was poured onto water (130 mL) and extracted with ethyl acetate (30 mL). The organic layers were washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography on silica, eluting with methylene chloride / methanol (95/5) followed by methylene chloride / methanol containing ammonia (1%) (90/10). The fractions containing the expected product were combined and evaporated. The residue was triturated with diethylether (2 mL), collected by filtration, washed with diethylether (1 mL) and dried under vacuum at 50°C to give 212 mg of **37** (74%). ^{1}H NMR: δ 3.96 (s, 3H); 5.31 (s, 2H); 7.32 (s, 1H); 7.4 (d, 1H); 7.45 (t, 2H); 7.5-7.6 (m, 4H); 7.85 (s, 1H); 8.35 (br s, 1H); 9.55 (br s, 1H). MS-ESI *m/z* 428 $[MH]^+$.

***N*-(2-Fluoro-4-methylphenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine 41 (Procedure L).** A solution of *N*-7-Benzyloxy-(2-fluoro-4-methylphenyl)-6-methoxy-4-quinazolinylamine **35** (2 g, 4.7 mmol) in TFA (20 mL) was heated at 80 °C for 5 h and stirred at ambient temperature overnight. The volatiles were removed under vacuum and the residue was suspended in water (50 mL). Solid sodium hydrogen carbonate was added until the pH was approximately 7. The precipitate was then collected by filtration, washed with water and

dried under vacuum. The solid was purified by column chromatography eluting with methanol / methylene chloride (5/95). After removal of the solvent by evaporation, the solid was triturated with diethylether (5 mL), collected by filtration, washed with diethylether (2 mL) and dried under vacuum to give 1.04 g of **41** (74%). ^{1}H NMR: δ 2.4 (s, 3H), 4.0 (s, 3H), 7.15 (d, 1H), 7.22 (s, 1H), 7.25 (d, 1H), 7.41 (t, 1H), 8.05 (s, 1H), 8.7 (s, 1H), 11.0 (s, 1H), 11.5-11.8 (br s, 1H). MS-ESI *m/z* 300 $[MH]^+$.

***N*-(4-Cyano-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine 42 (Procedure J).** A solution of *N*-7-Benzyloxy-(4-cyano-2-fluorophenyl)-6-methoxy-4-quinazolinylamine **36** (5.4 g, 13.5 mmol) in TFA (50 mL) was refluxed for 2 h. After cooling the volatile was removed under vacuum and the residue was azeotroped with toluene. The residue was dissolved in ethylacetate (50 mL) and washed with saturated aqueous sodium bicarbonate. The organic layer was separated, washed with brine and dried ($MgSO_4$). The volatiles was removed under vacuum and the residue was dried under vacuum to give 4 g of **42** (95%).(purity 90% measured by NMR). ^{1}H NMR ($DMSOd_6$, CF_3COOD): δ 4.0 (s, 3H), 7.8-7.95 (m, 2H), 8.1 (s, 1H), 8.05-8.12 (m, 1H), 8.88 (s, 1H).

***N*-(4-Chloro-2,6-difluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine 43 (Procedure J).** A solution of *N*-7-Benzyloxy-(4-chloro-2,6-difluorophenyl)-6-methoxy-4-quinazolinylamine **37** (200 mg, 0.47 mmol) in TFA (3 mL) was stirred at 80 °C for 3 h. After cooling, the volatiles were removed under vacuum and the residue was dissolved in water containing methanol (5%). The pH was adjusted to 8 with sodium hydrogen carbonate and the solid was collected by filtration and washed with water. The solid was solubilised in a mixture of ethyl acetate / methanol / methylene chloride (47/6/47). The solution was filtered and the filtrate was evaporated under vacuum to give 126 mg of **43** (80%). ^{1}H NMR: δ 3.95 (s, 3H), 7.1 (s, 1H), 7.55 (d, 2H), 7.8 (s, 1H), 8.3 (s, 1H), 9.42 (br s, 1H). MS-ESI *m/z* 338 $[MH]^+$.

***tert*-butyl 4-[2-({4-[(4-bromo-2-fluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]piperidine-1-carboxylate 46 (Procedure E).** To a suspension of *N*-(4-bromo-

2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **40**[18] (1.3 g, 3.57 mmol), triphenylphosphine (2.34 g, 8.9 mmol), *tert*-butyl 4-(hydroxyethyl)piperidine-1-carboxylate **53**[20] (1.22 g, 5.36 mmol) and triphenylphosphine (2.34 g, 8.9 mmol) in methylene chloride (15 mL) was added diethylazodicarboxylate (1.4 mL, 8.9 mmol). The mixture was stirred for 2 h at ambient temperature. The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride / methanol 99/1 followed by 98/2. The fractions containing the expected product were combined and evaporated to give 2 g of **46** (Contaminated by triphenylphosphine oxide. Purity ~ 80%. Used crude in the next step). MS-ESI *m/z* 575-577 [MH]+

***tert*-butyl 4-[2-({4-[(2-fluoro-4-methylphenyl)amino]-6-methoxyquinazolin-7-yl}oxy)methyl]piperidine-1-carboxylate 47 (Procedure E).** Triphenylphosphine (2.19 g, 8.36 mmol) was added to a suspension of *N*-(2-fluoro-4-methylphenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **41** (1 g, 3.34 mmol) in methylene chloride (10 mL) cooled at 0 °C, followed by *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate **52**[20] (1.08 g, 5.01 mmol) and diethyl azodicarboxylate (1.31mL, 8.36 mmol). After stirring for 2 h at ambient temperature, the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride / methanol (2/98). After removal of the solvent by evaporation, the residue was triturated with diethylether (2 mL), collected by filtration, washed with diethylether (1 mL) and dried under vacuum to give 327 mg of **47** (20%). ^{1}H NMR: δ 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.0-2.1 (m, 1H), 2.4 (s, 3H), 2.75-2.9 (br s, 2H), 3.95 (s, 3H), 4.0 (br s, 2H), 4.05 (d, 2H), 7.1 (d, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.85 (t, 1H), 8.32 (s, 1H), 9.45 (s, 1H). MS-ESI *m/z* 497 $[MH]^+$.

***tert*-butyl 4-[({4-[(4-bromo-2,6-difluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)methyl]piperidine-1-carboxylate 48 (Procedure F).** Triphenylphosphine (1.71 g, 6.54 mmol) was added to a suspension of *N*-(4-bromo-2,6-difluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **44** (1 g, 2.62 mmol) in methylene chloride (10 mL) cooled at 0 °C, followed by *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate **52**[20] (845 mg, 3.93

mmol) and diethylazodicarboxylate (1.03 mL, 6.54 mmol). After stirring 2 h at ambient temperature, triphenylphosphine (0.68 g, 2.6 mmol), diethyl azodicarboxylate (412 µL, 2.62 mmol) and *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate **52** (563 mg, 2.62 mmol) were added. After stirring 1 h at ambient temperature, the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride / methanol (2/98). After removal of the solvent by evaporation, the residue was triturated with diethylether (2 mL), collected by filtration, washed with diethylether (1 mL) and dried under vacuum to give 620 mg of **48** (41%). ^{1}H NMR: δ 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.0-2.1 (m, 1H), 2.7-2.9 (m, 2H), 3.95 (s, 3H), 4.0 (br s, 2H), 4.05 (d, 2H), 7.22 (s, 1H), 7.65 (d, 2H), 7.85 (s, 1H), 8.35 (s, 1H), 9.4-9.6 (br s, 1H). MS-ESI *m/z* 579-581 $[MH]^+$.

***tert*-butyl 4-[({4-[(4-chloro-2,6-difluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)methyl]piperidine-1-carboxylate 49 (Procedure E).** Triphenylphosphine (250 mg, 0.88 mmol) was added to a suspension of *N*-(4-chloro-2,6-difluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **43** (150 mg, 0.44 mmol) in methylene chloride cooled at 0 ^{0}C, followed by *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate **52**[20] (150 mg, 0.88 mmol) and diethyl azodicarboxylate (210 mg, 0.88 mmol). After stirring 2 h at ambient temperature, the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride /methanol 98/2 followed by 95/5. The fractions containing the expected product were combined and evaporated. The residue was triturated with diethylether (1 mL), filtered, washed with diethylether (1 mL) and dried under vacuum to give 113 mg of **49** (59%). ^{1}H NMR: δ 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.0-2.1 (m, 1H), 2.7-2.9 (m, 2H), 3.95 (s, 3H), 4.0 (br s, 2H), 4.05 (d, 2H), 7.2 (s, 1H), 7.6 (m, 2H), 7.8 (s, 1H), 8.35 (s, 1H), 9.4-9.6 (br s, 1H). MS-ESI m/z 535 $[MH]^+$.

7-(2-(piperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one 59. A solution of 7-(2-(1-*tert*butoxycarbonylpiperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one **57** (10.5 g, 20 mmol) in methylene

chloride (100 mL) containing TFA (25 mL) was stirred for 1 h at ambient temperature. Water (50 mL) and methylene chloride (100 mL) were added and the pH of the aqueous layer was adjusted to 8 with solid sodium hydrogen carbonate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with diethylether (20 mL) and the solid was filtered and dried under vacuum to give 8.3 g of **59** (100 %). ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 9H), 1.65 (m, 2H), 1.9 (br s, 2H), 1.8-1.9 (m, 1H), 2.0 (d, 2H), 2.9 (t, 2H), 3.45 (d, 2H), 4.0 (s, 3H), 4.2 (t, 2H), 5.95 (s, 2H), 7.1 (s, 1H), 7.65 (s, 1H), 8.2 (s, 1H).

6-methoxy-7-[(1-methylpiperidin-4-yl)ethoxy]-3,4-dihydroquinazolin-4-one 63. A solution of 7-(2-(1-methylpiperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one **61** (4.2 g, 9.7 mmol) in methanol saturated with ammonia (150 mL) was stirred overnight at ambient temperature. The volatiles were removed under vacuum and the residue was triturated with diethylether (10 mL). The solid was filtered, washed with diethylether (5 mL) and dried under vacuum to give 3.12 g of **63** (100 %). ^{1}H NMR: δ 1.3 (m, 2H), 1.58 (br s, 1H), 1.72 (dd, 2H), 1.8 (d, 2H), 2.4 (s, 3H), 2.2-2.45 (m, 2H), 3.0 (br s, 2H), 3.85 (s, 3H), 4.15 (t, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H). MS-ESI *m/z* 318 $[MH]^+$.

4-Chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)ethoxy]quinazoline 65. A solution of 6-methoxy-7-[(1-methylpiperidin-4-yl)ethoxy]-3,4-dihydroquinazolin-4-one **63** (3.1 g , 9.8 mmol) in thionyl chloride (40 mL) containing DMF (400 µL) was refluxed for 4 h. After cooling, the volatiles were removed under vacuum. The residue was partitioned between methylene chloride (15 mL) and water and the pH of the aqueous layer was adjusted to 11 with solid sodium hydrogen carbonate and aqueous ammonia. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was triturated with diethylether (10 mL), filtered, washed with diethylether (5 mL) and dried under vacuum to give 1.83 g of **65** (54 %). ^{1}H NMR ($CDCl_3$): δ 1.4-1.7 (m, 3H), 1.8 (d, 2H), 1.9 (dd, 2H), 2.05 (t, 2H), 2.35 (s, 3H), 2.95 (d, 2H), 4.05 (s, 3H), 4.25 (t, 2H), 7.3 (s, 1H), 7.4 (s, 1H), 8.88 (s, 1H). MS-ESI *m/z* 336 $[MH]^+$. Anal. ($C_{17}H_{22}N_3O_2Cl$) C, H, N.