

Supporting information :

Procedure A :

***N*-(4-chlorophenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 3** (346 mg, 89%); $^1\text{H NMR}$ δ 4.02 (s, 3H, CH_3O), 4.03 (s, 3H, CH_3O), 7.32 (s, 1H, H8), 7.6 (d, 2H, H2' and H6'), 7.8 (d, 2H, H3' and H5'), 8.25 (s, 1H, H5), 8.84 (s, 1H, H2). $^{13}\text{C NMR}$ δ 56.4 ($\text{O}-\underline{\text{C}}\text{H}_3$), 57.0 ($\text{O}-\underline{\text{C}}\text{H}_3$), 99.7 (C8), 104.1 (C5), 107.3 (C10), 126.4 (C2' or C3' and 5' or 6'), 128.6 (C3' or C2' and 5' or 6'), 130.1 (C4'), 135.6 (C4), 135.9 (C1'), 148.6 (C2), 150.2 (C9), 156.3 (C7), 158.1 (C6). MS -ESI m/z 316 [MH]⁺. Anal. ($\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_3\text{Cl} \cdot 1.1 \text{HCl}$) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 4** (383 mg, 93%); $^1\text{H NMR}$ δ 4.01 (s, 6H, 2 CH_3O), 7.33 (s, 1H, H8), 7.45 (dd, 1H, H3'), 7.64 (t, 1H, H6'), 7.68 (dd, 1H, H5'), 8.2 (s, 1H, H5), 8.8 (s, 1H, H2). $^{13}\text{C NMR}$ δ 56.5 ($\text{O}-\underline{\text{C}}\text{H}_3$), 57.0 ($\text{O}-\underline{\text{C}}\text{H}_3$), 99.5 (C8), 104.2 (C5), 106.9 (C10), 116.9 (d, C3', J C-F = 24.1 Hz), 123.7 (d, C1', J C-F = 12.3 Hz), 124.9 (d, C5', J C-F = 4.1 Hz), 129.9 (C6'), 132.3 (d, C4', J C-F = 9.8 Hz), 135.5 (C4), 148.6 (C2), 150.3 (C9), 156.6 (C7), 156.8 (d, C2', J C-F = 252.2 Hz), 158.9 (C6). MS -ESI m/z 334 [MH]⁺. Anal. ($\text{C}_{16}\text{H}_{13}\text{O}_2\text{N}_3\text{FCl} \cdot 1.23 \text{HCl}$) C, H, N.

***N*-(3-hydroxyphenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 5** (337 mg, 91%); $^1\text{H NMR}$ δ 4.02 (s, 6H, 2 CH_3O), 6.75 (d, 1H, H6'), 7.1 (d, 1H, H4'), 7.15 (s, 1H, H2'), 7.3 (t, 1H, H5'), 7.31 (s, 1H, H8), 8.2 (s, 1H, H5), 8.82 (s, 1H, H2), 9.73 (bs, 1H, NH or OH), 11.0 (bs, 1H, NH or OH). $^{13}\text{C NMR}$ δ 56.4 ($\text{O}-\underline{\text{C}}\text{H}_3$), 57.0 ($\text{O}-\underline{\text{C}}\text{H}_3$), 99.4 (C8), 104.2 (C5), 107.1 (C10), 112.3 (C4'), 113.6 (C6'), 115.6 (C2'), 129.2 (C5'), 135.0 (C4), 137.8 (C1'), 148.3 (C2), 150.1 (C9), 156.1 (C7), 157.6 (C3'), 158.1 (C6). MS -ESI m/z 298 [MH]⁺. Anal. ($\text{C}_{16}\text{H}_{15}\text{O}_3\text{N}_3 \cdot 1.0 \text{HCl}, 0.5 \text{H}_2\text{O}$) C, N; H : calc 4.44 found 4.9.

***N*-(2-fluoro-4-iodophenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 6** (452 mg, 88%); $^1\text{H NMR}$ δ 4.02 (s, 6H, 2 CH_3O), 7.34 (s, 1H, H5), 7.38 (t, 1H, H6'), 7.72 (d, 1H, H5'), 7.9 (d, 1H, H3'), 8.2 (s, 1H, H8), 8.8 (s, 1H, H2). $^{13}\text{C NMR}$ δ 56.5

(O-CH₃), 56.8 (O-CH₃), 92.7 (C4'), 99.8 (C8), 103.9 (C5), 106.9 (C10), 124.5 (d, C1'), 125.0 (d, C3'), 130.3 (C6' or C5'), 133.8 (C5' or C6'), 135.8 (C4), 148.8 (C2), 150.3 (C9), 156.5 (d, C2'), 156.6 (C7), 158.8 (C6). MS-ESI *m/z* 426 [MH]⁺. Anal. (C₁₆H₁₃O₂N₃FI. 0.88 HCl, 0.7 H₂O) C, H, N.

***N*-(2-chloro-4-iodophenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 7** (417 mg, 79%); ¹H NMR δ 4.04 (s, 6H, 2 CH₃O), 7.35 (d, 1H, H6'), 7.4 (s, 1H, H8'), 7.85 (dd, 1H, H5'), 8.06 (s, 1H, H8), 8.3 (s, 1H, H5), 8.78 (s, 1H, H2). ¹³C NMR δ 56.5 (O-CH₃), 56.9 (O-CH₃), 93.9 (C4'), 99.3 (C8), 104.1 (C5), 106.8 (C10), 131.4 (C6'), 132.4 (C2' or C4'), 134.3 (C1'), 135.4 (C4' or C2'), 136.9 (C5'), 137.7 (C3'), 148.5 (C2), 150.3 (C9), 156.6 (C7), 159.1 (C6). MS-ESI *m/z* 442 [MH]⁺. Anal. (C₁₆H₁₃O₂N₃ClI. 1.1 HCl) C, H, N.

***N*-(2,4-difluorophenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 8** (356 mg, 91%); ¹H NMR δ 3.99 (s, 3H, CH₃O), 4.0 (s, 3H, CH₃O), 7.25 (t, 1H, H5'), 7.30 (s, 1H, H8), 7.5 (t, 1H, H3'), 7.62 (td, 1H, H3'), 8.15 (s, 1H, H5), 8.77 (s, 1H, H2). ¹³C NMR δ 56.5 (O-CH₃), 57.0 (O-CH₃), 99.5 (C8), 104.2 (C5), 104.7 (dd, C3', *J* C-F = 24.6 Hz and 27.7 Hz), 106.9 (C10), 111.8 (dd, C5' or C6', *J* C-F = 22.7 Hz and 4.2 Hz), 121.1 (dd, C6' or C5', *J* C-F = 12.9 and 4.2 Hz), 129.9 (d, C1', *J* C-F = 8.3 Hz), 135.4 (C4), 148.7 (C2), 150.3 (C9), 156.6 (C7), 157.1 (dd, C2', *J* C-F = 251.1 Hz and 12.6 Hz), 159.2 (C6), 161.0 (dd, C4', *J* C-F = 247.7 Hz and 11.1 Hz). MS-ESI *m/z* 318 [MH]⁺. Anal. (C₁₆H₁₃O₂N₃F₂. 1.2 HCl, 0.2 H₂O) C, H, N.

***N*-(3-chloro-4-fluorophenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 9** (394 mg, 96%); ¹H NMR δ 4.0 (s, 3H, CH₃O), 4.01 (s, 3H, CH₃O), 7.31 (s, 1H, H8), 7.55 (t, 1H, H2'), 7.75 (m, 1H, H6'), 8.05 (d, 1H, H5'), 8.23 (s, 1H, H5), 8.85 (s, 1H, H2). MS-ESI *m/z* 334 [MH]⁺. Anal. (C₁₆H₁₃O₂N₃FCl. 1.2 HCl, 0.26 H₂O) C, H, N.

***N*-(2-fluoro-5-hydroxy-4-methylphenyl)-6,7-dimethoxy-4-quinazolinylamine hydrochloride 10** (326 mg, 90%); m.p. > 250^oC, ¹H NMR δ 2.15 (s, 3H, CH₃), 3.99 (s, 6H, 2 CH₃O), 6.88 (d, 1H, H6' or H3'), 7.10 (d, 1H, H6' or H3'), 7.32 (s, 1H, H8),

8.2 (s, 1H, H5), 8.78 (s, 1H, H2), 9.66 (s, 1H, NH or OH). Anal. (C₁₇H₁₆N₃FO₃·1HCl, 0.65 iPrOH) C, H, N.

***N*-(3-hydroxyphenyl)-6-methoxy-7-(2-methoxyethoxy)-4-quinazolinylamine hydrochloride 12.** To a mixture of 3-aminophenol (111 mg, 1.02 mmol) in 2-propanol (6 mL) was added 5.5 N. hydrogen chloride in 2-propanol (0.2 mL) followed by 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline **56** (250 mg, 0.94 mmol). After heating at 80°C for 4 h, the mixture was cooled and ether (5 mL) was added. The solid was filtered, washed with ether (2 X 5 mL) and dried under vacuum overnight at 50°C to give 326 mg of **12** (93%). ¹H NMR δ 3.35 (s, 3H, CH₃O), 3.8 (m, 2H, CH₂O), 4.02 (s, 3H, CH₃O), 4.30 (m, 2H, CH₂O), 6.75 (dd, 1H, H6'), 7.10 (t, 1H, H4'), 7.19 (s, 1H, H2'), 7.24 (t, 1H, H5'), 7.44 (s, 1H, H8), 8.33 (s, 1H, H5), 8.8 (s, 1H, H2). ¹³C NMR δ 57.0 (Ph-O-CH₃), 58.3 (CH₂-O-CH₃), 68.3 (CH₂-O-Ph), 69.7 (CH₂-O-CH₃), 100.1 (C8), 104.3 (C5), 107.2 (C10), 112.0 (C4'), 113.5 (C6'), 115.5 (C2'), 129.3 (C5'), 135.0 (C4), 137.7 (C1'), 148.4 (C2), 150.1 (C9), 155.4 (C7), 157.6 (C3'), 158.1 (C6). MS-ESI *m/z* 342 [MH]⁺. Anal. (C₁₈H₁₉O₄N₃·1.1 HCl, 0.23 H₂O) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-nitro-4-quinazolinylamine hydrochloride 64.** A solution of 4-chloro-6-methoxy-7-nitroquinazoline hydrochloride **63** (7.4 g, 26 mmol) and 2-fluoro-4-chloroaniline (4.3 g, 29 mmol) in isopropanol (100 mL) was refluxed for 3 h. After cooling, the solid was filtered, washed with 2-propanol, followed by ether and dried under vacuum to give 10.2 g of **64** (99%). m.p. 198-200°C. ¹H NMR δ 4.12 (s, 3H, CH₃O), 7.45 (d, 1H, H3'), 7.6 (dd, 1H, H6'), 7.68 (d, 1H, H5'), 8.45 (s, 1H, H5), 8.75 (s, 1H, H2 or H8), 8.8 (s, 1H, H2 or H8). MS-ESI *m/z* 349 [MH]⁺. Anal. (C₁₅H₁₀ClFN₄O₂·1 HCl) C, H.

***N*-(2-fluoro-5-methoxycarbonyloxy-4-methylphenyl)-6-methoxy-7-nitro-4-quinazolinylamine hydrochloride 65.** A mixture of 4-chloro-6-methoxy-7-nitroquinazoline hydrochloride **63** (784 mg, 2.8 mmol) and 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (621 mg, 3.1 mmol) in 2-propanol (10 mL) was heated at reflux for 2 h. The mixture was allowed to cool, the precipitated product

collected by filtration, washed with 2-propanol, ether and dried under vacuum to give 1.12 g of **65** (90%). $^1\text{H NMR}$ δ 2.22 (s, 3H, CH_3CO), 3.86 (s, 3H, CH_3O), 4.10 (s, 3H, CH_3O), 7.41 (d, 1H, H3' or H6'), 7.46 (d, 1H H3' or H6'), 8.40 (s, 1H, H5), 8.55 (s, 1H, H8), 8.77 (s, 1H, H2), 11.4 (br s, 1H). MS-ESI m/z 403 $[\text{MH}]^+$.

Procedure B :

***N*-(4-chloro-2-fluorophenyl)-6,7-di-(2-methoxyethoxy)-4-quinazolinylamine hydrochloride 14**. To a solution of ***N*-(4-chloro-2-fluorophenyl)-6,7-dihydroxy-4-quinazolinylamine 59** (0.15 g, 0.44 mmol) in DMF (3 mL) was added potassium carbonate (0.181 g, 1.3 mmol) followed by 2-methoxy-1-bromoethane (43 μL , 0.46 mmol). After stirring 1 h at 30°C, potassium carbonate (0.12 g, 0.88 mmol) followed by 2-methoxy-1-bromoethane (45 μL , 0.48 mmol) were added. After stirring overnight at 30°C the mixture was partitioned between ethyl acetate and water. The water layer was further extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (MgSO_4), filtered and evaporated. The resulting product was purified by column chromatography eluting with a mixture of methylene chloride and methanol (98/2). After removal of the volatile components, the oil was triturated in a mixture of petroleum ether and ether. The resulting precipitate was filtered, and washed with ether. The solid was dissolved in methylene chloride and 2N. hydrogen chloride in ether was added (3 mL). The solid was filtered, washed with ether and dried under vacuum to give 82 mg of **14** (41%). $^1\text{H NMR}$ ($\text{DMSO-}d_6$, CF_3COOD) δ 3.38 (s, 6H, 2 CH_3), 3.8 (bs, 4H, 2 CH_2), 4.32 (t, 2H, CH_2O), 4.37 (t, 2H, CH_2O), 7.35 (s, 1H, H8), 7.45 (d, 1H, H3'), 7.63 (t, 1H, H5' or H6'), 7.68 (d, 1H, H5' or H6'), 8.11 (s, 1H, H5), 8.9 (s, 1H, H2). MS-ESI m/z 422 $[\text{MH}]^+$. Anal. ($\text{C}_{20}\text{H}_{21}\text{ClFN}_3\text{O}_4 \cdot 1 \text{HCl}$) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-[2-(4-morpholinyl)-ethoxy]-4-quinazolinylamine hydrochloride 21**. 4-(2-Chloroethyl)morpholine hydrochloride (40 mg, 2.1 mmol) was added to ***N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine 47** (63 mg, 0.2 mmol) and potassium carbonate (95 mg, 0.69 mmol) in DMF (3mL) and the mixture heated at 100°C for 3 h. The mixture was allowed to cool, the volatiles were removed by evaporation and the residues

partitioned between water and methylene chloride. The organic phase was separated, passed through phase separating paper and the solvent was removed by evaporation. The residue was dissolved in acetone, and 1N. hydrogen chloride in ether (0.2 mL) was added. The precipitated product was collected by filtration and dried to give 50 mg of **21** (50%). ^1H NMR (DMSO- d_6 , CF_3COOD) δ 3.3 (t, 2H, CH_2N), 3.6 (d, 2H, CH_2N -morpholine), 3.75 (t, 2H, CH_2N -morpholine), 3.8 (t, 2H, CH_2O -morpholine), 4.0 (d, 2H, CH_2O -morpholine), 4.05 (s, 3H, CH_3O), 4.7 (t, 2H, CH_2O), 7.45 (d, 1H, $\text{H}_{3'}$), 7.5 (s, 1H, H_8), 7.65 (t, 1H, $\text{H}_{6'}$), 7.7 (dd, 1H, $\text{H}_{5'}$), 8.3 (s, 1H, H_5), 8.9 (s, 1H, H_2). ^{13}C NMR δ 51.9 (2C, $\underline{\text{C}}\text{H}_2\text{-N-}\underline{\text{C}}\text{H}_2$), 54.5 ($\text{CH}_2\text{-}\underline{\text{C}}\text{H}_2\text{-N}$), 57.2 (Ph-O- $\underline{\text{C}}\text{H}_3$), 63.2 (2C, $\underline{\text{C}}\text{H}_2\text{-O-}\underline{\text{C}}\text{H}_2$), 64.2 (Ph-O- $\underline{\text{C}}\text{H}_2$), 101.1 (C8), 104.64 (C5), 107.6 (C10), 116.9 (d, C3', $J\text{C-F} = 22.7$ Hz), 123.8 (d, C1', $J\text{C-F} = 11.7$ Hz), 125.0 (d, C5', $J\text{C-F} = 4.3$ Hz), 129.8 (C6'), 132.3 (d, C4', $J\text{C-F} = 10.1$ Hz), 136.7 (C4), 149.0 (C2), 150.2 (C9), 154.6 (C7), 156.8 (d, C2', $J\text{C-F} = 252.7$ Hz), 159.0 (C6). MS - ESI m/z 433 $[\text{MH}]^+$. Anal. ($\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3\text{FCl} \cdot 2.0 \text{ HCl}$) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-[3-(4-morpholinyl)-propoxy]-4-quinazolinylamine hydrochloride 22.** 4-(3-Chloropropyl)morpholine⁶⁷ (2.26 g, 13.8 mmol) was added to *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **47** (2.21 g, 6.9 mmol) and potassium carbonate (6.5 g, 47 mmol) in DMF (100mL). The mixture was heated at 110°C for 4 h and then allowed to cool. The volatile components were removed by evaporation and the residue was partitioned between water and methylene chloride. The organic phase was separated, washed with brine, passed through phase separating paper and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol/ aqueous ammonia (100/8/1). The product was dissolved in acetone and isopropanol and 1N. hydrogen chloride in ether (4.8mL) was added. The precipitated product was collected by filtration and washed with acetone and ether to give 2.16 g of **22** (65%). m.p. 193-196°C. ^1H NMR (DMSO- d_6 , CF_3COOD) δ 2.35 (m, 2H, CH_2), 3.15 (t, 2H, CH_2N), 3.35 (t, 2H, CH_2N -morpholine), 3.37 (d, 2H, CH_2N -morpholine), 3.72 (t, 2H, CH_2O -morpholine), 4.02 (s, 3H, CH_3O), 4.1 (d, 2H, CH_2O -morpholine), 4.35 (t, 2H, CH_2O), 7.4 (s, 1H, H_8), 7.5 (d, 1H, $\text{H}_{3'}$), 7.65 (t, 1H, $\text{H}_{6'}$), 7.7 (dd, 1H, $\text{H}_{5'}$), 8.15 (s, 1H, H_5), 8.9 (s, 1H,

H2). ^{13}C NMR δ 22.9 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 51.3 (2C, $\text{CH}_2\text{-N-CH}_2$), 53.7 ($\text{N-CH}_2\text{-CH}_2$), 56.3 (Ph-O-CH_3), 63.4 (2C, $\text{CH}_2\text{-O-CH}_2$), 66.2 (Ph-O-CH_2), 102.5 (C8), 107.2 (C5), 108.7 (C10), 116.6 (d, C3', $J_{\text{C-F}} = 10.0$ Hz), 129.3 (C6'), 130.1 (d, C4', $J_{\text{C-F}} = 10$ Hz), 145.7 (C9), 148.9 (C6), 152.9 (C7), 153.4 (C2), 156.6 (d, C2', $J_{\text{C-F}} = 251.0$ Hz), 157.9 (C4). MS - ESI m/z 447 $[\text{MH}]^+$. Anal. ($\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_3\text{FCl} \cdot 1.0 \text{ HCl}, 0.5 \text{ C}_3\text{H}_6\text{O}$) H, N; C : calc 55.1 found 54.7.

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-[(4-pyridyl)-methoxy]-4-**

quinazolinylamine hydrochloride 26. A mixture of *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **47** (320 mg, 1 mmol), potassium carbonate (414 mg, 3 mmol), potassium iodide (40 mg) and 4-(chloromethyl)pyridine hydrochloride (250 mg, 1.5 mmol) in DMF (15mL) was heated at 60°C for 2 h. The mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried (MgSO_4) and the solvent removed by evaporation. The residue was suspended in ethanol (20 mL) and concentrated hydrogen chloride (0.5 mL) was added. The volatile components were removed by evaporation and the solid residue was azeotroped with toluene. The solid product was recrystallised from 2-propanol to give 335 mg of **26** (70%). m.p. 232-234°C. ^1H NMR δ 4.1 (s, 3H, CH_3O), 5.69 (s, 2H, CH_2O), 7.46 (dd, 1H, H3'), 7.52 (s, 1H, H8), 7.62 (t, 1H, H6'), 7.69 (dd, 1H, H5'), 8.03 (d, 2H, CH pyridine), 8.55 (s, 1H, H5), 8.83 (s, 1H, H2), 8.93(d, 2H, CH-N=CH pyridine). ^{13}C NMR δ 57.3 (Ph-O-CH_3), 68.3 (Ph-O-CH_2), 101.2 (C8), 105.0 (C5), 107.7 (C10), 116.9 (d, C3', $J_{\text{C-F}} = 23.6$ Hz), 101.2 (C8), 105.0 (C5), 107.7 (C10), 116.9 (d, C3', $J_{\text{C-F}} = 23.6$ Hz), 123.7 (d, C1', $J_{\text{C-F}} = 13.0$ Hz), 124.1 (2C, pyridyl C12), 125.0 (d, C5', $J_{\text{C-F}} = 2.4$ Hz), 129.9 (C6'), 132.4 (d, C4', $J_{\text{C-F}} = 8.5$ Hz), 135.2 (C4), 143.4 (2C, pyridyl C13), 148.9 (C2), 150.4 (C9), 153.7 (pyridyl C11), 154.5 (C7), 156.8 (d, C2', $J_{\text{C-F}} = 251.9$ Hz), 159.1 (C6). MS - ESI m/z 411 $[\text{MH}]^+$. Anal. ($\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}_2\text{ClF} \cdot 0.5 \text{ H}_2\text{O}, 1.95 \text{ HCl}$) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-7-(4-chlorobutoxy)-6-methoxy-4-quinazolinylamine**

72. A solution of *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **47** (0.35 g, 1.1 mmol), 1-bromo-4-chlorobutane (190 μL , 1.6 mmol), potassium carbonate (453 mg, 3.2 mmol) in DMF (10 mL) was stirred at 40°C for 5 h. The mixture was partitioned between water and methylene chloride and the

pH was adjusted to 7 with 2N. hydrogen chloride. The organic layer was separated, washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with methylene chloride / ethyl acetate (1/1). After removal of the volatiles, the residue was triturated with a mixture of pentane/ ether, filtered, washed with pentane and dried under vacuum to give 233 mg of **72** (51%). m.p. 176-179°C. ¹H NMR (DMSO-d₆, CF₃COOD) δ 2.05 (bs, 4H, CH₂CH₂), 3.76 (t, 2H, CH₂O), 4.02 (s, 3H, CH₃O), 4.28 (t, 2H, CH₂Cl), 7.3 (s, 1H, H₈), 7.45 (d, 1H, H_{3'}), 7.62 (t, 1H, H_{6'}), 7.68 (dd, 1H, H_{5'}), 8.1 (s, 1H, H₅), 8.88 (s, 1H, H₂). ¹³C NMR δ 26.1 (OCH₂CH₂), 29.1 (ClCH₂CH₂), 45.3 (ClCH₂), 56.4 (OCH₃), 67.9 (CH₂O), 102.3 (C₅), 107.5 (C₈), 108.7 (C₁₀), 116.7 (d, C_{3'}, J C-F = 23.9 Hz), 124.8 (d, C_{5'}, J F-C = 3.7 Hz), 126.1 (d, C_{1'}, J F-C = 11.1 Hz), 129.4 (C_{6'}), 130.2 (d, C_{4'}, J F-C = 11.1 Hz), 146.6 (C₇), 149.3 (C₆), 152.9 (C₉), 153.9 (C₂), 156.4 (d, C_{2'}, J F-C = 233.3), 158.0 (C₄). MS-ESI *m/z* 410 [MH]⁺. Anal. (C₁₉H₁₈Cl₂FN₃O₂) C, H, N.

3-methoxy-4-(2-methoxyethoxy)acetophenone 74. A solution of **4-hydroxy-3-methoxyacetophenone 73** (20 g, 120 mmol) and 2-bromoethyl methyl ether (12.4 mL, 130 mmol) in DMF (400 mL) containing potassium carbonate (49.8 g, 360 mmol) was heated at 50°C overnight. After cooling, the reaction mixture was diluted with water and adjusted to pH = 2. After extraction with ethyl acetate, the organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by flash chromatography using petroleum ether/ethyl acetate (6/4 followed by 1/1) as eluent to give 21.8 g of **74** (81%). m.p. 84-86°C. ¹H NMR (CDCl₃) δ 2.6 (s, 3H, CH₃CO), 3.45 (s, 3H, CH₃OCH₂), 3.8 (t, 2H, CH₂O), 3.92 (s, 3H, CH₃O), 4.25 (t, 2H, CH₂O), 6.9 (d, 1H, H₅), 7.5-7.6 (m, 2H, H₂ and H₆). MS-ESI *m/z* 224 [M]⁺. Anal. (C₁₂H₁₆O₄) C, H, N.

Procedure D :

N-(4-chloro-2-fluorophenyl)-6-methoxy-7-(2-methoxyethoxy)-4-quinolinylamine hydrochloride 17. A solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline hydrochloride **78** (3 g, 9.8 mmol) and 4-chloro-2-fluoroaniline (2.2 mL, 19.6 mmol) in DMF (50mL) was heated at 150°C for 30 min. After dilution with 2-propanol (50mL), the precipitate was collected by filtration, washed with 2-propanol and dried

under vacuum to give 2.05 g of **17** (50%). m.p. 282-284°C. ¹H NMR δ 3.37 (s, 3H, CH₃O), 3.8 (t, 2H, CH₂O), 4.03 (s, 3H, CH₃), 4.35 (t, 2H, CH₂O), 6.5 (d, 1H, H₃), 7.52 (s, 1H, H₈), 7.54 (d, 1H, H_{3'}), 7.68 (dd, 1H, H_{5'}), 7.8 (d, 1H, H_{6'}), 8.2 (s, 1H, H₅), 8.42 (d, 1H, H₂), 10.72 (br s, 1H, NH). ¹³C NMR δ 56.7 (Ph-O-CH₃), 58.2 (CH₂-O-CH₃), 68.3 (Ph-O-CH₂), 69.8 (CH₂-O-CH₃), 99.7 (C₈), 100.5 (C₅), 102.7 (C₁₀), 111.6 (C₃), 117.7 (d, C_{3'}, *J* C-F = 24.3 Hz), 124.2 (d, C_{1'}, *J* C-F = 11.5 Hz), 126.0 (d, C_{5'}, *J* C-F = 3.3 Hz), 130.1 (C_{6'}), 132.7 (d, C_{4'}, *J* C-F = 10.1 Hz), 135.2 (C₄), 140.03 (C₂), 149.7. MS - ESI *m/z* 337 [MH]⁺. Anal. (C₁₉H₁₈N₂O₃ClF·0.34 H₂O, 0.95 HCl, 0.08 iPrOH, 0.04 DMF) C, H, N.

***N*-(4-chloro-2-fluoro-5-hydroxyphenyl)-6-methoxy-7-(2-methoxyethoxy)-4-cinnolinylamine hydrochloride 18.** A solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)cinnoline **83** (0.2 g, 0.74 mmol) and 4-chloro-2-fluoro-5-hydroxyaniline (132 mg, 0.82 mmol) in DMF (2.5mL) was heated at 150°C for 45 min. After cooling, the solid was filtered off, washed with 2-propanol, ether and dried under vacuum to give 157 mg of **18** (49%). m.p. 296-299°C. ¹H NMR (DMSO-d₆, CF₃COOD) δ 3.4 (s, 3H, CH₃O), 3.85 (t, 2H, CH₂O), 4.1 (s, 3H, CH₃O), 4.4 (t, 2H, CH₂O), 7.2 (d, 1H, H_{3'}), 7.45 (s, 1H, H₈), 7.65 (d, 1H, H_{6'}), 8.05 (s, 1H, H₃), 8.35 (d, 1H, H₅). ¹³C NMR δ 57.1 (Ph-O-CH₃), 58.3 (CH₂-O-CH₃), 68.8 (Ph-O-CH₂), 69.7 (CH₃-O-CH₂), 98.0 (C₈), 101.5 (C₅), 112.0 (C₁₀), 114.4 (C_{6'}), 118.2 (d, C_{3'}, *J* C-F = 23.5 Hz), 119.3 (d, C_{4'}, *J* C-F = 10.7 Hz), 122.8 (d, C_{1'}, *J* C-F = 13.7 Hz), 129.5 (C₃), 138.5 (C₄), 143.9 (C₆), 149.1 (d, C_{2'}, *J* C-F = 240.93), 150.6 (d, C_{5'}, *J* C-F = 2.5 Hz), 152.1 (C₉), 155.8 (C₇). MS - ESI *m/z* 394 [MH]⁺. Anal. (C₁₈H₁₇N₃O₄ClF·1.0 HCl) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-(2-methoxyethoxy)-4-cinnolinylamine hydrochloride 19.** A solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)cinnoline **83** (0.4 g, 1.5 mmol) and 4-chloro-2-fluoroaniline (282 μL, 2.5 mmol) in DMF (5mL) was heated at 150°C for 20 min. After cooling, 2-propanol (15mL) was added and resulting solid filtered off, washed with 2-propanol and dried under vacuum to give 450 mg of **19** (72%). m.p. 279-281°C. ¹H NMR (DMSO-d₆, CF₃COOD) 3.35 (s, 3H, CH₃O), 3.8 (t, 2H, CH₂O), 4.05 (s, 3H, CH₃O), 4.4 (t, 2H, CH₂O), 7.4 (s, 1H, H₈), 7.5

(d, 1H, H3'), 7.7 (t, 1H, H6'), 7.75 (d, 1H, H5'), 8.05 (s, 1H, H3), 8.3 (s, 1H, H5). ¹³C NMR δ 57.1 (CH₃-O-Ph), 58.3 (CH₂-O-CH₃), 68.9 (Ph-O-CH₂), 69.7 (CH₃-O-CH₂), 98.2 (C8), 101.3 (C10), 112.1 (C10), 117.9 (d, C3', J C-F = 23.7 Hz), 123.2 (d, C1', J C-F = 12.1 Hz), 126.1 (d, C5', J C-F = 3.1 Hz), 129.4 (C3), 129.5 (C6'), 133.0 (d, C4', J C-F = 10.0 Hz), 138.7 (C4), 144.0 (C9), 152.2 (C7), 155.8 (C6), 156.6 (d, C2', J C-F = 253.6 Hz). MS - ESI *m/z* 378 [MH]⁺. Anal. (C₁₈H₁₇N₃O₃ClF. 1.0 HCl) C, H, N.

Procedure E :

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-[(3-thienyl)-methoxy]-4-quinazolinylamine hydrochloride 25.** Diethyl azodicarboxylate (197 μL, 1.2 mmol) was added dropwise to a solution of *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **47** (200 mg, 0.6 mmol), 3-hydroxymethyl thiophene (107 mg, 0.93 mmol) and triphenylphosphine (328 mg, 1.2 mmol) in methylene chloride (6mL) cooled at 0°C. The mixture was stirred for 2 h at ambient temperature and further triphenylphosphine (157 mg, 0.57 mmol), 3-hydroxymethyl thiophene (107 mg, 0.93 mmol) and diethylazodicarboxylate (98.5 μL, 0.59 mmol) were added. The mixture was stirred for 2 h at ambient temperature and the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with water and brine, dried (MgSO₄) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/ethyl acetate (4/6). The resulting oil was dissolved in ether and a 5N solution of hydrogen chloride in 2-propanol (1mL) was added. The resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give 59 mg of **25** (20%). m.p. 250-255°C. ¹H NMR δ 3.99 (s, 3H, CH₃O), 5.34 (s, 2H, CH₂O-Ar), 7.25 (d, 1H, Thiophene H4), 7.43 (d, 1H, H3'), 7.45 (s, 1H, H8), 7.58-7.63 (m, 2H, H6' and Thiophene H2), 7.7 (dd, 1H, H5'), 7.72 (d, 1H, Thiophene H5), 8.17 (s, 1H, H5'), 8.78 (s, 1H, H2). MS - ESI *m/z* 416 [MH]⁺. Anal. (C₂₀H₁₅N₃O₂ClFS. 0.95 HCl) C, H, N.

***N*-(4-bromo-2,6-difluorophenyl)-6-methoxy-7-[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinazolinylamine hydrochloride 35.** To a solution of 2-hydroxyethyl-1-(1,2,3-

triazole) (66 mg, 0.588 mmol) in methylene chloride (4 mL) was added *N*-(4-bromo-2,6-difluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **48** (150 mg, 0.39 mmol) and triphenylphosphine (308 mg, 1.17 mmol) and diethylazodicarboxylate (185 μ L, 1.17 mmol). After stirring for 1 h at ambient temperature, triphenylphosphine (103 mg, 0.39 mmol), 2-hydroxyethyl-1-(1,2,3-triazole) (44 mg, 0.39 mmol) and diethylazodicarboxylate (562 μ L, 0.39 mmol) was added. After stirring for 3 h at ambient temperature, the mixture was purified by chromatography. The crude mixture was poured onto silica and eluted with a mixture of methylene chloride / ether / methanol 50/43/7. After evaporation of the solvent, the oil was dissolved in methylene chloride / methanol and 2.2 N hydrogen chloride in ether (1 mL) was added. The solution was concentrated to 1/3 of its volume and the solid was filtered, washed with ether and dried under vacuum to give 85 mg of **35** (42 %).

^1H NMR (DMSO- d_6 , CF_3COOD) δ 3.99 (s, 3H, CH_3O), 4.70 (t, 2H, CH_2O), 4.96 (t, 2H, CH_2N), 7.37 (s, 1H, H8), 7.76 (d, 2H, H3' and H5'), 7.78 (s, 1H, triazole), 8.09 (s, 1H, triazole), 8.21 (s, 1H, H5), 8.92 (s, 1H, H2). ^{13}C NMR δ 48.3 ($\text{N}-\underline{\text{C}}\text{H}_2$), 57.0 ($\text{Ph}-\text{O}-\underline{\text{C}}\text{H}_3$), 67.6 ($\text{Ph}-\text{O}-\underline{\text{C}}\text{H}_2$), 101.4 (C8), 104.1 (C5), 107.5 (C10), 113.9 (t, C1' or C4'), 116.2 (dd, C3', $J_{\text{C-F}} = 25.2$ Hz and 1.8 Hz), 120.5 (t, C4' or C1', $J_{\text{C-F}} = 11.4$ Hz), 125.3 (triazole C5), 133.4 (triazole C4), 136.5 (C4), 149.2 (C9), 150.4 (C2), 155.1 (C7), 157.9 (dd, C2', $J_{\text{C-F}} = 251.7$ and 5.2 Hz), 159.2 (C6). MS-ESI m/z 479 [MH] $^+$. Anal. ($\text{C}_{19}\text{H}_{15}\text{BrF}_2\text{N}_6\text{O}_2 \cdot 0.4 \text{H}_2\text{O} \cdot 0.9 \text{HCl}$) C, H, N.

Procedure G :

N-(4-chloro-2-fluorophenyl)-6-methoxy-7-[2-(1*H*-1,2,3-triazol-1-yl)ethoxy]-4-quinazolinylamine hydrochloride **30**. To a solution of *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **47** (2.24 g, 7 mmol) in methylene chloride (60 mL) was added triphenyl phosphine (5.5 g, 21 mmol), followed by a solution of 2-hydroxyethyl-1-(1,2,3-triazole)⁷¹ (1.2 g, 10.5 mmol) in methylene chloride (5 mL) and diethylazodicarboxylate dropwise (3.65 g, 21 mmol). After stirring 2 h at ambient temperature, ether (20 mL) was added. The precipitate was filtered, washed with a mixture of methylene chloride / ether 1/1 and dried. The solid was dissolved in methylene chloride / methanol (20 mL / 20 mL) and 3.5 N hydrogen chloride in ether (4 mL) was added. The solution was diluted with ether (50 mL) and the precipitate was filtered, washed with ether and dried under vacuum to

give 2.35 g of **30** (69 %). ¹H NMR (DMSO-d₆, CF₃COOD) δ 3.99 (s, 3H, CH₃O), 4.68 (t, 2H, CH₂O), 4.96 (t, 2H, CH₂N), 7.4 (s, 1H, H₈), 7.45 (d, 1H, H₃'), 7.62 (t, 1H, H₆'), 7.7 (d, 1H, H₅'), 7.8 (s, 1H, triazole), 8.2 (bs, 1H, triazole), 8.22 (s, 1H, H₅), 8.86 (s, 1H, H₂). ¹³C NMR δ 48.5 (N-CH₂), 56.2 (Ph-O-CH₃), 66.9 (Ph-O-CH₂), 102.3 (C₅), 108.2 (C₈), 108.9 (C₁₀), 116.6 (d, C₃', J C-F = 23.7 Hz), 124.6 (d, C₅', J C-F = 3.8 Hz), 125.2 (triazole C₅), 125.9 (d, C₁', J C-F = 12.6 Hz), 129.2 (d, C₆', J C-F = 2.2 Hz), 129.9 (d, C₄', J C-F = 9.8 Hz), 133.3 (triazole C₄), 146.7 (C₉), 148.9 (C₆), 152.8 (C₇ or C₂), 153.0 (C₂ or C₇), 156.9 (C₄), 157.0 (d, C₂', J C-F = 252.5 Hz). MS -ESI *m/z* 415 [MH]⁺. Anal. (C₁₉H₁₆ClFN₆O₂ · 1.2 HCl, 0.3 H₂O) C, H, N.

***N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-[2-[*N*-methyl-*N*-(4-pyridyl)]amine]ethoxy]-4-quinazolinylamine hydrochloride **28**.**

Triphenylphosphine (5.5 g, 21 mmol) followed by 2-[*N*-methyl-*N*-(4-pyridyl)]aminoethanol **90** (1.49 g, 9.8 mmol) were added to a stirred solution of *N*-(4-chloro-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine **47** (2.23 g, 7 mmol) in methylene chloride (60 mL) under nitrogen. Diethylazodicarboxylate (3.65 g, 21 mmol) was then added dropwise and the mixture was stirred at ambient temperature for 2 h. Ethyl acetate (200 mL) was added and the mixture was stirred for a further 2 h. The solid product was collected by filtration, washed with ethyl acetate, dried under vacuum and finally purified by column chromatography eluting with methylene chloride/methanol (75/25 followed by 60/40 and 50/50) to give a white solid. The purified product was dissolved in methylene chloride/methanol and the insoluble removed by filtration. 3N. hydrogen chloride in ether (10 mL) was added to the filtrate and the volatiles were removed by evaporation. The residue was triturated with ether and the solid product collected by filtration and dried under vacuum to give 2.75 g of **28** (75%). m.p. 222-227°C. ¹H NMR (DMSO-d₆, CF₃COOD) δ 3.29 (s, 3H, NCH₃), 3.95 (s, 3H, CH₃O), 4.16 (t, 2H, CH₂N), 4.48 (t, 2H, CH₂O), 7.05 (br s, 1H, H₈), 7.37 (s, 2H, pyridyl CH), 7.42 (d, 1H, H₃'), 7.58 (t, 1H, H₆'), 7.65 (dd, 1H, H₅'), 8.18 (s, 1H, H₅), 8.28 (br s, 2H, pyridyl CH-N=CH), 8.86 (s, 1H, H₂). MS -ESI *m/z* 454 [MH]⁺. Anal. (C₂₃H₂₁N₅O₂ClF · 0.9 H₂O, 2.0 HCl) C, H, N.

7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride 41. A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one **40** (2.82 g, 10 mmol), thionyl chloride (40 mL) and DMF (0.28 mL) was stirred and heated at reflux for 1 h. The volatiles were removed by evaporation, the residue was azeotroped with toluene to give 3.45 g of **41** (3.45g). ^1H NMR δ 4.0 (s, 3H, CH_3O), 5.37 (s, 2H, CH_2O), 7.35-7.45 (m, 4H, Ph), 7.52 (d, 1H, Ph), 7.50 (s, 1H, H8 or H5), 7.58 (s, 1H, H8 or H5), 8.9 (s, 1H, H2). ^{13}C NMR δ 56.2 (CH_2O), 70.6 (OCH_3), 102.4 (C5), 108.0 (C8), 118.6 (C10), 128.1 (2 C12), 128.3 (C14), 128.5 (2 C13), 137.3 (C11), 148.5 (C9), 151.5 (C7), 152.2 (C2), 155.6 (C6), 157.9 (C4). MS-ESI m/z 301 [MH] $^+$.

For the microanalysis, a sample of **41** was partitioned between methylene chloride and water. The pH of the aqueous layer was adjusted to 8 with sodium bicarbonate. The organic layer was separated, washed with brine, dried (MgSO_4), filtered, evaporated and dried under vacuum to give **41 free base**. Anal. ($\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl} \cdot 0.23 \text{H}_2\text{O}$) C, H, N.

4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline 56. A solution of 6-methoxy-7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one **55** (750 mg, 3 mmol) in thionyl chloride (7.5 mL) containing DMF (75 μL) was refluxed for 1h. After removal of the volatile under vacuum, toluene was added and the solvent was evaporated. The solid was suspended in methylene chloride / water (5 mL / 5mL) and the pH of the aqueous layer was adjusted to 7-8 with solid sodium bicarbonate. The organic layer was separated, washed with water followed by brine, dried (MgSO_4), filtered and evaporated. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 645 mg of **56** (80%). ^1H NMR δ 3.3 (s, 3H, CH_3O), 3.75 (t, 2H, CH_2O), 4.04 (s, 3H, CH_3O), 4.35 (t, 2H, CH_2O), 7.4 (s, 1H, H8 or H5), 7.47 (s, 1H, H8 or H5), 8.87 (s, 1H, H2). ^{13}C NMR δ 56.1 (Ph-O- CH_3), 58.2 ($\text{CH}_2\text{-O-CH}_3$), 68.5 (Ph-O- CH_2), 69.8 ($\text{CH}_2\text{-O-CH}_3$), 102.2 (C5), 107.4 (C8), 118.5 (C10), 148.4 (C6), 151.3 (C7), 152.0 (C2), 155.8 (C9), 157.8 (C4). MS-ESI m/z 269 [MH] $^+$. Anal. ($\text{C}_{12}\text{H}_{13}\text{O}_3\text{N}_2\text{Cl} \cdot 0.14 \text{H}_2\text{O}$) C, H, N.

4-chloro-6-methoxy-7-[2-[1-(1,2,3-triazolyl)]ethoxy]quinazoline 58. A solution of 6-methoxy-7-[2-[1-(1,2,3-triazolyl)]ethoxy]quinazoline **57** (920 mg, 3.2 mmol) in thionyl chloride (10 mL) containing DMF (0.9 mL) was heated at 80°C for 1 h. After

evaporation of the volatiles, the residue was azeotroped with toluene. The residue was partitioned between ethyl acetate and water and the aqueous layer was adjusted to pH = 8 with solid bicarbonate. The organic layer was washed with water, brine, dried (MgSO_4), and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (96/4) to give 693 mg of **58** (71%). ^1H NMR (CDCl_3) δ 4.1 (s, 3H, CH_3O), 4.55 (t, 2H, CH_2O), 4.95 (t, 2H, CH_2N), 7.3 (s, 1H, triazole), 7.4 (s, 1H, H8), 7.75 (s, 1H, triazole), 7.95 (s, 1H, H5), 8.85 (s, 1H, H2). MS-EI m/z 305 $[\text{MH}]^+$. Anal. ($\text{C}_{13}\text{H}_{12}\text{N}_5\text{O}_2\text{Cl}$) C, H, N.

4-chloro-6-methoxy-7-nitroquinazoline hydrochloride 63. A suspension of **6-methoxy-7-nitro-3,4-dihydroquinazolin-4-one 62** (8 g, 36 mmol) in thionyl chloride (150 mL) and DMF (0.8 mL) was heated at reflux for 3 h. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene. The resulting solid was triturated with ether, collected by filtration and dried under vacuum to give 7.5 g of **63** (75%). ^1H NMR δ 4.13 (s, 3H, CH_3O), 7.8 (s, 1H, H8), 8.7 (s, 1H, H5), 9.13 (s, 1H, H2).

4-chloro-7-(2-methoxyethoxy)quinazoline hydrochloride 71. A solution of **7-(2-methoxyethoxy)-3,4-dihydroquinazolin-4-one 70** (500 mg, 2.2 mmol) in thionyl chloride (15 mL) and DMF (0.1 mL) was heated at reflux for 3 h. The volatiles were removed by evaporation to give 520 mg of **71** as a cream solid (83%). ^1H NMR ($\text{DMSO}-d_6$, CF_3COOD) δ 3.33 (s, 3H, CH_3O), 3.74 (t, 2H, CH_2O), 4.30 (t, 2H, CH_2O), 7.3 (s, 1H, H8), 7.33 (d, 1H, H6), 8.12 (d, 1H, H5), 9.19 (s, 1H, H2). MS-EI m/z 238 $[\text{M}]^+$. Anal. ($\text{C}_{11}\text{H}_{11}\text{ClN}_2\text{O}_2 \cdot 0.75 \text{HCl}$) C, H, N.

4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline hydrochloride 78. A solution of **6-methoxy-7-(2-methoxyethoxy)-1,4-dihydroquinolin-4-one 77** (500 mg, 2 mmol) in thionyl chloride (10 mL) and DMF (3 drops) was heated at reflux for 1 h. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene and then triturated with ether. The solid was collected by filtration and dried under vacuum to give 590 mg of **78** (95%). ^1H NMR δ 3.36 (s, 3H, CH_3OCH_2), 3.8 (t, 2H, CH_2O), 4.05 (s, 3H, CH_3OPh), 4.35 (t, 2H, CH_2O), 7.51 (s, 1H, H8), 7.68 (s, 1H,

H5), 7.91 (d, 1H, H2), 8.85 (d, 1H, H3). ^{13}C NMR δ 55.8 (Ph-O- $\underline{\text{C}}\text{H}_3$), 58.2 (CH₂-O- $\underline{\text{C}}\text{H}_3$), 67.9 (Ph-O- $\underline{\text{C}}\text{H}_2$), 70.0 (CH₃-O- $\underline{\text{C}}\text{H}_2$), 101.2 (C8), 108.8 (C5), 119.6 (C3), 120.9 (C10), 138.9 (C4), 145.6 (C6), 147.7 (C2), 150.6 (C9), 152.0 (C7). MS-ESI m/z 268 [MH]⁺. Anal. (C₁₃H₁₄ClNO₃ · 0.3 HCl) C, H, N.

Procedure J

***N*-7-benzyloxy-(4-bromo-2,6-difluorophenyl)-6-methoxy-4-quinazolinylamine hydrochloride 43.** A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride **41** (337 mg, 1 mmol), 4-bromo-2,6-difluoroaniline (416 mg, 2 mmol) in 2-pentanol (8 mL) was refluxed for 70 min. After cooling to ambient temperature, the precipitate was filtered, washed with isopropanol followed by ether and dried under vacuum to give 264 mg of **43** (51%). Used without purification in the next step. MS-ESI m/z : 472-474 [MH]⁺. ^1H NMR (DMSO-*d*₆, CF₃COOD) δ 4.05 (s, 3H, CH₃O), 5.4 (s, 2H, CH₂O), 7.3-7.55 (m, 5H, Ph, H3', H5' and H8), 7.75 (d, 2H, Ph), 8.25 (s, 1H, H5), 8.9 (s, 1H, H2).

***N*-7-benzyloxy-(4-bromo-2-fluorophenyl)-6-methoxy-4-quinazolinylamine hydrochloride 44.** A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline **41** (8.35 g, 27.8 mmol), and 4-bromo-2-fluoroaniline (5.65 g, 29.7 mmol) in 2-propanol (200 mL) was heated at reflux for 4 h. The resulting precipitate was collected by filtration, washed with 2-propanol and then ether and dried under vacuum to give 9.46 g of **44** (78%). ^1H NMR (DMSO-*d*₆, CD₃COOD) δ 4.0 (s, 3H, CH₃O), 5.37 (s, 2H, CH₂O), 7.35-7.5 (m, 4H), 7.52-7.62 (m, 4H), 7.8 (d, 1H, H5'), 8.14 (s, 1H, H5), 8.79 (s, 1H, H2). ^{13}C NMR δ 56.9 (Ph-O- $\underline{\text{C}}\text{H}_3$), 70.7 (Ph-O- $\underline{\text{C}}\text{H}_2$), 100.9 (C8), 104.2 (C5), 107.1 (C10), 119.7 (d, C3', $J_{\text{C-F}} = 23.9$ Hz), 120.2 (d, C4', $J_{\text{C-F}} = 9.2$ Hz), 124.1 (d, C1', $J_{\text{C-F}} = 12.9$ Hz), 127.9 (d, C5', $J_{\text{C-F}} = 3.7$ Hz), 128.3 (2C, C13), 128.4 (C14), 128.6 (2C, C12), 130.2 (C6'), 135.2 (C11), 135.6 (C4), 148.9 (C2), 150.5 (C9), 155.5 (C7), 156.8 (d, C2', $J_{\text{C-F}} = 253.7$ Hz), 158.9 (C6). MS-ESI m/z 456 [MH]⁺. Anal. (C₂₂H₁₇N₃O₂BrF · 0.9HCl) C, H, N.

***N*-7-benzyloxy-(4-chloro-2-fluoro-5-hydroxyphenyl)-6-methoxy-4-quinazolinylamine hydrochloride 45.** A mixture of 4-chloro-2-fluoro-5-

hydroxyaniline (2.5 g, 15 mmol) and 7-benzyloxy-4-chloro-6-methoxyquinazoline **41** (4.2 g, 14 mmol) in 2-propanol was heated at reflux for 2 h. The mixture was then allowed to cool and the solid product collected by filtration, washed with 2-propanol and dried to give 4.8 g of **45** (81%). m.p. 322-323 °C. ¹H NMR δ 3.98 (s, 3H, CH₃O), 5.18 (s, 2H, CH₂O), 7.05 (d, 1H, H3'), 7.18-7.27 (m, 7H), 8.06 (s, 1H, H5), 8.38 (s, 1H, H2). MS-ESI *m/z* 426 [MH]⁺. Anal. (C₂₂H₁₇N₃ClFO₃ · 0.15H₂O, 0.4 iPrOH, 1.0 HCl) C, H, N.

Procedure K :

***N*-(4-bromo-2,6-difluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine 48.**

A suspension of ***N*-(7-benzyloxy-(4-bromo-2,6-difluorophenyl)-6-methoxy-4-quinazolinylamine hydrochloride 43** (264 mg, 0.51 mmol) in TFA (5 mL) was refluxed for 1 h. After cooling, toluene was added and the volatile were removed under vacuum. The oily residue was dissolved in ethanol (5 mL) and adjusted to pH=7 with an aqueous solution of sodium bicarbonate. The precipitate was filtered, washed with water, followed by ethanol and ether and dried under vacuum to give 137 mg of **48** (70%). ¹H NMR (DMSO-*d*₆, CF₃COOD) δ 4.01 (s, 3H, CH₃O), 7.3 (s, 1H, H8), 7.77 (d, 2H, H3' and H5'), 8.07 (s, 1H, H5), 8.85 (s, 1H, H2). ¹³C NMR δ 56.0 (CH₃O), 102.2 (C5), 105.4 (C10), 107.7 (C8), 115.8 (d, C3' and C5', *J* C-F = 25.7 Hz), 116.3 (C1' or C4'), 118.0 (C4' or C1'), 146.8 (C9), 148.3 (C7), 152.5 (C2), 153.9 (C6), 157.1 (C4), 158.3 (d, C2' et C6', *J* C-F = 270.2 Hz). MS-ESI *m/z* 383 [MH]⁺. Anal. (C₁₅H₁₀N₃F₂BrO₂) C, H.

***N*-(4-bromo-2-fluorophenyl)-7-hydroxy-6-methoxy-4-quinazolinylamine 49.** A

solution of ***N*-(4-bromo-2-fluorophenyl)-7-benzyloxy-6-methoxy-4-quinazolinylamine hydrochloride 44** (9.4g, 19.1 mmol) in TFA (90 mL) was heated at reflux for 50 min. The mixture was allowed to cool and was poured on to ice. The resulting precipitate was collected by filtration and dissolved in methanol (70 mL). The solution was adjusted to pH = 9-10 with concentrated aqueous ammonia solution. The mixture was concentrated to half initial volume by evaporation. The resulting precipitate was collected by filtration, washed with water and then ether, and dried under vacuum to give 5.66 g of **49** (82%). ¹H NMR (DMSO-*d*₆, CD₃COOD) 3.95 (s,

3H, CH₃O), 7.09 (s, 1H, H3'), 7.48 (s, 1H, H8), 7.54 (t, 1H, H6'), 7.64 (d, 1H, H5'), 7.79 (s, 1H, H5), 8.31 (s, 1H, H2). ¹³C NMR δ 56.0 (CH₂O), 102.2 (C5), 107.9 (C10), 110.0 (C8), 117.3 (d, C4', J C-F = 7.4 Hz), 119.2 (d, C3', J C-F = 23.9 Hz), 126.5 (d, C1', J C-F = 12.9 Hz), 127.4 (C6'), 129.5 (C5'), 146.9 (C7), 148.7 (C6), 152.7 (C2), 153.0 (C9), 156.6 (d, C2', J C-F = 251.9 Hz), 156.8 (C4). MS-ESI *m/z* 366 [MH]⁺. Anal. (C₁₅H₁₁N₃O₂BrF) C, H, N

Procedure L

6-methoxy-3-(pivaloyloxymethyl)-7-[2-[1-(1,2,3-triazolyl)]ethoxy]-3,4-dihydroquinazolin-4-one 54. Triphenylphosphine (2.82 g, 10.7 mmol) was added to a solution of 2-(1,2,3-triazol-1-yl)ethanol⁷¹ (609 mg, 5.4 mmol) and **7-hydroxy-6-methoxy-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-4-one 52** (1.1 g, 3.6 mmol), in methylene chloride (70 mL) and diethylazodicarboxylate (600 μL, 10.7 mmol) was then added. After stirring for 2 h at ambient temperature, volatiles were removed by evaporation, and the residue was purified by column chromatography eluting with methylene chloride/methanol (98/2) to give 4 g of **54** (97%). ¹H NMR δ 1.15 (s, 9H, C(CH₃)₃), 3.88 (s, 3H, CH₃O), 4.6 (t, 2H, CH₂O), 4.89 (t, 2H, CH₂O), 5.9 (s, 2H, OCH₂N), 7.24 (s, 1H, H8), 7.51 (s, 1H, H5), 7.77 (s, 1H, triazole), 8.2 (s, 1H, triazole), 8.35 (s, 1H, H2).

Procedure M

6-methoxy-7-[2-[1-(1,2,3-triazolyl)]ethoxy]-3,4-dihydroquinazolin-4-one 57. 5.1M Ammonia in methanol (30 mL) was added to a solution of **6-methoxy-3-(pivaloyloxymethyl)-7-[2-(1-(1,2,3-triazolyl)ethoxy)]-3,4-dihydroquinazolin-4-one 54** (1.4 g, 3.5 mmol) in methanol (30 mL). After stirring overnight at ambient temperature, the volatiles were removed by evaporation, and the residue triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 946 mg of **57** (92%). ¹H NMR (DMSO-d₆, CF₃COOD) δ 3.9 (s, 3H, CH₃O), 4.6 (t, 2H, CH₂O), 4.9 (t, 2H, CH₂N), 7.25 (s, 1H, H8), 7.52 (s, 1H, H5), 7.77 (s, 1H, triazole), 8.19 (s, 1H, triazole), 8.9 (s, 1H, H2). MS-ESI *m/z* 170 [MH]⁺.