Electronic supplementary information

Chemistry

Starting materials and reagents were obtained from commercial suppliers and were used without purification. Melting points were determined in open capillary tubes on a Büchi reference B–530 digital melting point apparatus and were uncorrected. Kieselgel 60 F–254 commercial plates were used for analytical TLC with UV light and/or iodine used to follow the course of the reaction. Silica gel Kieselgel Si 60, 0.063–0.200 mm (Merck) was used for column chromatography. The structures of all compounds were determined by IR (using a Bruker VECTOR 22 instrument) and ^{1}H–NMR (300 MHz) spectra were recorded on a Bruker AC300P NMR spectrophotometer in DMSO–[D_6] or in $CDCl_3$ at room temperature. APCI+ (Atmospheric Pressure Chemical Ionization) mass spectra were obtained on a Thermo Electon Surveyor MSQ LC–MS system.

5.1 4–Chloro–6,7–dimethoxyquinazoline (4).[30] To a solution of methyl–2–amino–4,5–dimethoxybenzoate (4.0 g, 19.0 mmol) in *N,N*–dimethylformamide (40 mL) and methanol (10 mL), formamide (76.0 mmol) and sodium methoxide (54.0 mmol) were added. The resulting mixture was refluxed for 16 h. After quench by water (100 mL), the mixture was neutralized by 1M HCl solution. The precipitated was collected by filtration, washed with H_2O (30 mL) and Et_2O (30 mL) and dried *in vacuo* to give quinazolinone **3** as a white solid (82%) which was used directly in the next step. A mixture of **3** (3.0 g, 15.0 mmol) and phosphorous oxychloride (30 mL) was refluxed for 2 h. After removal of the solvent, the residue was dissolved in ice water (50 mL) and the mixture was neutralized by ammonium hydroxide. The precipitate was collected by filtration and dissolved in CH_2Cl_2 (100 mL). The organic layer

was washed with a 1M solution of K_2CO_3 (3 x 40 mL), brine (1 x 40 mL), dried over $CaCl_2$ and the solvent was removed under reduced pressure. Spectroscopic data for compound **4** is in agreement with that reported in the literature.[30]

5.2 General procedure for the one–pot synthesis of *N*–(4–aminophenyl) and *N*–(3–aminophenyl)carbamic acid ester derivatives (5–21).[31]

Method c: 4–nitrophenyl or 3–nitrophenyl isocyanate (1.0 g, 6.0 mmol) was dissolved in a mixture of dichloromethane /methanol (5/5) or ethanol (40 mL) and Raney nickel (400 mg) was added. The mixture was stirred under hydrogen at room temperature for 16 h. The product was filtered through a plug of Celite before being concentrated and purified by column chromatography on silica gel eluting with CH_2Cl_2/ethyl acetate (9/1).

Method d: 4–nitrophenyl isocyanate (1.0 g, 6.0 mmol) was dissolved in a mixture dichloromethane/THF (60 mL) and alcohol (60 mmole) with Raney nickel (400 mg) were added. The mixture was stirred under hydrogen at room temperature for 16 h. The product was filtered through a plug of Celite before being concentrated and purified by column chromatography on silica gel eluting with CH_2Cl_2/ethyl acetate (9/1).

***N*–(4–Aminophenyl)carbamic acid methyl ester (5).** Method c; (85%); white solid; Mp 89–91°C (recryst. petrolum ether). IR (ν, cm–1): 3382 (NH_2), 1710 (CO), 1265 (N–CO–O). ^{1}H NMR (DMSO–d_6): δ 3.67 (s, 3H, OCH_3); 5.78 (s, 2H, NH_2); 7.15 (d, J = 8.10 Hz, 2H, ArH); 7.61 (d, J = 8.10 Hz, 2H, ArH); 9.41 (s, 1H, NH). LC/MS ($APCI^+$) calcd for $C_8H_{10}N_2O_2$, m/z : 167 $(M+H)^+$.[31]

Spectroscopic data for compounds **6–21** were in agreement with those reported in the literature.[31]

5.3 General procedure for *N*–(4–amino–2,5–dichlorophenyl) ureas derivatives (22–23).

A solution of appropriate isocyanate (3.74 mmole, 1,1 eq) in anhydrous chloroform (15 mL) was added dropwise to a solution of 2,5–dichloro–1,4–phenylenediamine (0,60 g, 3,40 mmole) in anhydrous chloroform (35 mL). After stirring for 2 h at room temperature, the precipitated solid was filtered, then washed consecutively with chloroform, water and diethyl ether.

***N*–(4–Amino–2,5–dichlorophenyl)–*N'*–ethylurea (22).** (36%); white solid; Mp 101–103°C (recryst. toluene). IR (ν, cm–1): 3382 (NH_2), 1696 (CO), 1085 (C–Cl). ^{1}H NMR (DMSO–d_6): δ 1,06 (t, *J* = 7,30 Hz, 3H, CH_3); 3,12 (q, *J* = 7,30 Hz, 2H, CH_2); 5,25 (s, 2H, NH_2); 6,63 (s, 1H, NH); 6,83 (s, 1H, ArH); 7,61 (s, 1H, NH); 7,80 (s, 1H, ArH). LC/MS ($APCI^+$) calcd for $C_9H_{11}ClN_3O$, m/z : 249 $(M+H)^+$ – 251 $(M+2+H)^+$ – 253 $(M+4+H)^+$

***N*–(4–Amino–2,5–dichlorophenyl)–*N'*–butylurea (23).** (42%); white solid; Mp 88–90°C. IR (ν, cm–1): 3383 (NH_2), 1695 (CO), 1085 (C–Cl). ^{1}H NMR (DMSO–d_6): δ 0,89 (t, *J* = 7,30 Hz, 3H, CH_3); 1,20–1,45 (m, 4H, CH_2); 3,02 (t, *J* = 4,60 Hz, 2H, CH_2); 5,21 (s, 2H, NH_2); 6,61 (s, 1H, NH); 6,82 (s, 1H, ArH); 7,61 (s, 1H, NH); 7,81 (s, 1H, ArH). LC/MS ($APCI^+$) calcd for $C_{11}H_{15}ClN_3O$, m/z : 277 $(M+H)^+$ – 279 $(M+2+H)^+$ – 281 $(M+4+H)^+$

5.4 *N*–(4–Amino–2,5–dichlorophenyl)carbamic acid ethyl ester (24). Ethylchloroformate (3.74 mmole, 1,1 eq) was added dropwise at 0°C to a solution of 2,5–dichloro–1,4–phenylenediamine (0,60 g, 3,40 mmole) in anhydrous THF (20 mL). After stirring for 2 h at room temperature, the reaction was stopped by water (100 mL) and extracted by ethyl acetate

(3 x 70 mL). The organic layer was washed by $NaHCO_3$ saturated (120 mL), dried over $MgSO_4$ and evaporated under reduced pressure. 400 mg of **24** was thus obtained.

Yield 46%; brown solid; Mp 92–94°C. IR (ν, cm–1): 3383 (NH_2), 1711 (CO), 1264 (N–CO–O), 1086 (C–Cl). ^{1}H NMR (DMSO–d_6): δ 1,21 (t, *J* = 7,20 Hz, 3H, CH_3); 4,19 (q, *J* = 7,20 Hz, 2H, CH_2); 5,25 (s, 2H, NH_2); 6,62 (s, 1H, NH); 6,82 (s, 1H, ArH); 7,81 (s, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_9H_{11}Cl_2N_2O_2$, m/z : 250 $(M+H)^+$ – 252 $(M+2+H)^+$ – 254 $(M+4+H)^+$

5.5 General procedure for *N*–(4–amino–2–methylphenyl) amid derivatives (25–28).

To a solution of 2–methyl–4–nitroaniline (1g, 6,56 mmole) dissolved in toluene (20 mL) was added appropriate chloride (1,5 eq.) and the mixture was held to reflux for 5 h. The precipitate was collected by filtration, washed with petroleum ether and dried *in vacuo*. The 4–nitrophenyl amide was dissolved in a mixture of dichloromethane /methanol (5/5)(40 mL) and Raney nickel (400 mg) was added. The mixture was stirred under hydrogen at room temperature for 6 h. The product was filtered through a plug of Celite before being concentrated and purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1).

***N*–(4–Amino–2–methylphenyl)acetamid (25).** (58%); white solid; Mp 148–149°C. IR (ν, cm–1): 3382 (NH_2), 1641 (CO). ^{1}H NMR (DMSO–d_6): δ 1,97 (s, 3H, $COCH_3$); 2,02 (s, 3H, CH_3); 4,87 (s, 1H, NH_2); 6.30 (dd, *J* = 2.60 Hz and *J* = 8,40 Hz, 1H, ArH); 6,39 (d, *J* = 2,60 Hz, 1H, ArH); 6,83 (d, *J* = 8,40 Hz, 1H, ArH); 8,95 (s, 1H, NH). LC/MS (APCI$^+$) calcd for $C_9H_{12}N_2O$, m/z : 165 $(M+H)^+$

***N*–(4–Amino–2–methylphenyl)propionamid (26).** (69%); white solid; Mp 114–116°C. IR (ν, cm–1): 3381 (NH_2), 1640 (CO). ^{1}H NMR (DMSO–d_6): δ 1,02 (t, *J* = 7,30 Hz, 3H, CH_3);

2,00 (s, 3H, CH_3); 2,21 (q, *J* = 7,30 Hz, 2H, CH_2); 4,81 (s, 1H, NH_2); 6.30 (dd, *J* = 2.60 Hz and *J* = 8,40 Hz, 1H, ArH); 6,35 (d, *J* = 2,60 Hz, 1H, ArH); 6,81 (d, *J* = 8,40 Hz, 1H, ArH); 8,86 (s, 1H, NH). LC/MS ($APCI^+$) calcd for $C_{10}H_{14}N_2O$, m/z : 179 $(M+H)^+$

***N*–(4–Amino–2–methylphenyl)butanamid (27).** (59%); white solid; Mp 120–121°C. IR (ν, cm–1): 3381 (NH_2), 1642 (CO). ^1H NMR (DMSO–d_6): δ 0,95 (t, *J* = 7,30 Hz, 3H, CH_3); 1,61 (m, 2H, CH_2); 2,01 (s, 3H, CH_3); 2,20 (t, *J* = 4,30 Hz, 2H, CH_2); 4,83 (s, 1H, NH_2); 6.31 (dd, *J* = 2.30 Hz and *J* = 8,40 Hz, 1H, ArH); 6,39 (d, *J* = 2,30 Hz, 1H, ArH); 6,81 (d, *J* = 8,40 Hz, 1H, ArH); 8,88 (s, 1H, NH). LC/MS ($APCI^+$) calcd for $C_{11}H_{16}N_2O$, m/z : 193 $(M+H)^+$

***N*–(4–Amino–2–methylphenyl)pentanamid (28).** (56%); white solid; Mp 101–102°C. IR (ν, cm–1): 3381 (NH_2), 1642 (CO). ^1H NMR (DMSO–d_6): δ 0,91 (t, *J* = 7,30 Hz, 3H, CH_3); 1,31 (m, 2H, CH_2); 1,55 (m, 2H, CH_2); 2,00 (s, 3H, CH_3); 2,21 (t, *J* = 4,30 Hz, 2H, CH_2); 4,84 (s, 1H, NH_2); 6.31 (dd, *J* = 2.30 Hz and *J* = 8,10 Hz, 1H, ArH); 6,37 (d, *J* = 2,30 Hz, 1H, ArH); 6,81 (d, *J* = 8,10 Hz, 1H, ArH); 8,87 (s, 1H, NH). LC/MS ($APCI^+$) calcd for $C_{12}H_{18}N_2O$, m/z : 207 $(M+H)^+$

5.6 General procedure for compounds 29–50 by nucleophilic substitution of 4–Chloro–6,7–dimethoxyquinazoline (4).

The 4–chloro–6,7–dimethoxyquinazoline **4** (0,1 g, 0.45 mmmole) was dissolved in 2–propanol under reflux (4 mL) and the synthesized anilines **5–28** (1.2 eq.) were added. The mixture was then refluxed for 3–6 h. The precipitate was obtained by hot filtration, washed consecutively with 2–propanol and diethyl ether and purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (95/5).

{4–[6,7–Dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid ethyl ester chloride (29). (66%); yellow solid; Mp 194–196°C. IR (ν, cm–1): 3212 (NH) – 2465 (NH^+) – 1711 (CO) – 1265 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,21 (t, *J* = 7,20 Hz, 3H, CH_3); 3,97 (s, 3H, OCH_3); 4,00 (s, 3H, OCH_3); 4,15 (q, *J* = 7,20 Hz, 2H, CH_2); 7,37 (s, 1H ArH); 7,55 (m, 4H, ArH); 8,31 (s, 1H ArH); 8,78 (s, 1H ArH); 9,76 (s, 1H, NH); 11,38 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{20}N_4O_4$, m/z : 369 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid propyl ester chloride (30). (66%); yellow solid; Mp 192–194°C. IR (ν, cm–1): 3212 (NH) – 2468 (NH^+) – 1713 (CO) – 1265 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,91 (t, *J* = 7,20 Hz, 3H, CH_3); 1,62 (m, 2H, CH_2); 3,92 (s, 3H, OCH_3); 3,95 (s, 3H, OCH_3); 4,11 (t, *J* = 4,60 Hz, 2H, CH_2); 7,31 (s, 1H ArH); 7,52 (m, 4H, ArH); 8,25 (s, 1H ArH); 8,78 (s, 1H ArH); 9,77 (s, 1H, NH); 11,29 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{20}H_{22}N_4O_4$, m/z : 383 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid butyl ester chloride (31). (56%); yellow solid; Mp > 250°C. IR (ν, cm–1): 3213 (NH) – 2465 (NH^+) – 1711 (CO) – 1265 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,97 (t, *J* = 7,40 Hz, 3H, CH_3); 1,37 (m, 2H, CH_2); 1,61 (m, 2H, CH_2); 3,98 (s, 3H, OCH_3); 4,00 (s, 3H, OCH_3); 4,11 (t, *J* = 4,40 Hz, 2H, CH_2); 7,36 (s, 1H ArH); 7,52 (m, 4H, ArH); 8,30 (s, 1H ArH); 8,78 (s, 1H ArH); 9,77 (s, 1H, NH); 11,40 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{21}H_{24}N_4O_4$, m/z : 397 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}carbamic acid methyl ester chloride (32). (65%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3214 (NH) – 2466 (NH^+) – 1711 (CO) – 1264 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR

(DMSO–d_6): δ 2,22 (s, 3H, CH_3); 3,67 (s, 3H, OCH_3); 3,96 (s, 3H, OCH_3); 3,98 (s, 3H, OCH_3); 7,29 (s, 1H ArH); 7,45 (m, 3H, ArH); 8,19 (s, 1H ArH); 8,79 (s, 1H ArH); 8,95 (s, 1H, NH); 11,18 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{20}N_4O_4$, m/z : 369 $(M+H)^+$

{5–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}carbamic acid methyl ester chloride (33). (71%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3214 (NH) – 2466 (NH^+) – 1712 (CO) – 1265 (N–CO–O) – 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 2,22 (s, 3H, CH_3); 3,68 (s, 3H, OCH_3); 3,98 (s, 3H, OCH_3); 4,01 (s, 3H, OCH_3); 7,30 (s, 1H ArH); 7,45–7,50 (m, 3H, ArH); 8,15 (s, 1H ArH); 8,78 (s, 1H ArH); 9,03 (s, 1H, NH); 11,06 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{20}N_4O_4$, m/z : 369 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}carbamic acid ethyl ester chloride (34). (82%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3214 (NH) – 2465 (NH^+) – 1714 (CO) – 1264 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,26 (t, J = 7,30 Hz, 3H, CH_3); 2,22 (s, 3H, CH_3); 3,97 (s, 3H, OCH_3); 4,00 (s, 3H, OCH_3); 4,13 (q, J = 7,30 Hz, 2H, CH_2); 7,25 (s, 1H ArH); 7,45 (m, 3H, ArH); 8,12 (s, 1H ArH); 8,75 (s, 1H ArH); 8,91 (s, 1H, NH); 11,07 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{20}H_{22}N_4O_4$, m/z : 383 $(M+H)^+$

{5–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}carbamic acid ethyl ester chloride (35). (82%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3213 (NH) – 2465 (NH^+) – 1710 (CO) – 1265 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,25 (t, J = 7,20 Hz, 3H, CH_3); 2,21 (s, 3H, CH_3); 3,98 (s, 3H, OCH_3); 4,01 (s, 3H, OCH_3); 4,11 (q, J = 7,20 Hz, 2H, CH_2); 7,25 (s, 1H ArH); 7,45–7,55 (m, 3H, ArH); 8,29

(s, 1H ArH); 8,78 (s, 1H ArH); 9,02 (s, 1H, NH); 11,35 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{20}H_{22}N_4O_4$, m/z : 383 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}carbamic acid propyl ester chloride (36). (72%); white solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3214 (NH) – 2467 (NH^+) – 1710 (CO) – 1264 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,91 (t, *J* = 7,30 Hz, 3H, CH_3); 1,61 (m, 2H, CH_2); 2,23 (s, 3H, CH_3); 3,97 (s, 3H, OCH_3); 3,99 (s, 3H, OCH_3); 4,01 (m, 2H, CH_2); 7,31 (s, 1H ArH); 7,45 (m, 3H, ArH); 8,25 (s, 1H ArH); 8,75 (s, 1H ArH); 8,92 (s, 1H, NH); 11,29 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{21}H_{24}N_4O_4$, m/z : 397 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}carbamic acid butyl ester chloride (37). (77%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3213 (NH) – 2465 (NH^+) – 1711 (CO) – 1264 (N–CO–O) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,91 (t, *J* = 7,40 Hz, 3H, CH_3); 1,38 (m, 2H, CH_2); 1,60 (m, 2H, CH_2); 2,21 (s, 3H, CH_3); 3,95 (s, 3H, OCH_3); 3,97 (s, 3H, OCH_3); 4,12 (t, *J* = 4,70 Hz, 2H, CH_2); 7,31 (s, 1H ArH); 7,45 (m, 3H, ArH); 8,31 (s, 1H ArH); 8,72 (s, 1H ArH); 8,91 (s, 1H, NH); 11,38 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{22}H_{26}N_4O_4$, m/z : 411 $(M+H)^+$

{2–Chloro–4–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid methyl ester chloride (38). (63%); white solid; Mp > 250°C. IR (ν, cm–1): 3214 (NH) – 2467 (NH^+) – 1714 (CO) – 1262 (N–CO–O) – 1085 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 3,68 (s, 3H, OCH_3); 4,01 (s, 3H, OCH_3); 4,03 (s, 3H, OCH_3); 7,35 (s, 1H ArH); 7,65 (m, 2H, ArH); 7,91 (d, *J* = 2,00 Hz, 2H, ArH); 8,40 (s, 1H ArH); 8,84 (s, 1H ArH); 9,17 (s,

1H, NH); 11,59 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{18}H_{17}ClN_4O_4$, m/z : 389 $(M+H)^+$ – 391 $(M+2+H)^+$

{2–Chloro–5–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid methyl ester chloride (39). (66%); white solid; Mp > 250°C. IR (ν, cm–1): 3214 (NH) – 2465 (NH^+) – 1714 (CO) – 1261 (N–CO–O) – 1086 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 3,66 (s, 3H, OCH_3); 4,05 (s, 3H, OCH_3); 4,07 (s, 3H, OCH_3); 7,37 (s, 1H ArH); 7,63 (m, 2H, ArH); 7,92 (d, *J* = 2,10 Hz, 1H, ArH); 8,38 (s, 1H ArH); 8,81 (s, 1H ArH); 9,21 (s, 1H, NH); 11,50 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{18}H_{17}ClN_4O_4$, m/z : 389 $(M+H)^+$ – 391 $(M+2+H)^+$

{2–Chloro–4–[6,7–Dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid ethyl ester chloride (40). (71%); white solid; Mp > 250°C. IR (ν, cm–1): 3214 (NH) – 2467 (NH^+) – 1713 (CO) – 1262 (N–CO–O) – 1085 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,25 (t, *J* = 7,30 Hz, 3H, CH_3); 4,01 (s, 3H, OCH_3); 4,03 (s, 3H, OCH_3); 4,15 (q, *J* = 7,30 Hz, 2H, CH_2); 7,32 (s, 1H ArH); 7,67 (m, 2H, ArH); 7,92 (d, *J* = 2,30 Hz, 1H, ArH); 8,41 (s, 1H ArH); 8,86 (s, 1H ArH); 9,12 (s, 1H, NH); 11,59 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{19}ClN_4O_4$, m/z : 403 $(M+H)^+$ – 405 $(M+2+H)^+$

{2–Chloro–5–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid ethyl ester chloride (41). (81%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3214 (NH) – 2465 (NH^+) – 1714 (CO) – 1261 (N–CO–O) – 1086 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,21 (t, *J* = 7,40 Hz, 3H, CH_3); 4,02 (s, 3H, OCH_3); 4,04 (s, 3H, OCH_3); 4,12 (q, *J* = 7,40 Hz, 2H, CH_2); 7,35 (s, 1H ArH); 7,58 (m, 2H, ArH); 7,98 (d, *J* = 2,30 Hz, 1H, ArH); 8,33 (s, 1H ArH); 8,83 (s, 1H ArH); 9,20 (s, 1H, NH); 11,47 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{19}ClN_4O_4$, m/z : 403 $(M+H)^+$ – 405 $(M+2+H)^+$

{2–Chloro–4–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid propyl ester chloride (42). (54%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3214 (NH) – 2468 (NH^+) – 1712 (CO) – 1264 (N–CO–O) – 1086 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,91 (t, *J* = 7,30 Hz, 3H, CH_3); 1,61 (m, 2H, CH_2); 3,99 (s, 3H, OCH_3); 4,01 (s, 3H, OCH_3); 4,03 (m, 2H, CH_2); 7,33 (s, 1H ArH); 7,60–7,70 (m, 3H, ArH); 8,41 (s, 1H ArH); 8,84 (s, 1H ArH); 9,12 (s, 1H, NH); 11,55 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{20}H_{21}ClN_4O_4$, m/z : 417 $(M+H)^+$ – 419 $(M+2+H)^+$

{2–Chloro–4–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid butyl ester chloride (43). (75%); yellow solid; Mp > 250°C (Cyclohexan/Ethanol). IR (ν, cm–1): 3211 (NH) – 2468 (NH^+) – 1711 (CO) – 1266 (N–CO–O) – 1085 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,92 (t, *J* = 7,20 Hz, 3H, CH_3); 1,38 (m, 2H, CH_2); 1,60 (m, 2H, CH_2); 3,97 (s, 3H, OCH_3); 4,01 (s, 3H, OCH_3); 4,12 (t, *J* = 4,50 Hz, 2H, CH_2); 7,32 (s, 1H ArH); 7,60–7,75 (m, 3H, ArH); 8,42 (s, 1H ArH); 8,83 (s, 1H ArH); 9,12 (s, 1H, NH); 11,54 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{21}H_{23}ClN_4O_4$, m/z : 431 $(M+H)^+$ – 433 $(M+2+H)^+$

{2,5–Dichloro–4–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}carbamic acid ethyl ester chloride (44). (61%); white solid; Mp > 250°C. IR (ν, cm–1): 3212 (NH) – 2465 (NH^+) – 1711 (CO) – 1264 (N–CO–O) – 1085 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,28 (t, *J* = 7,20 Hz, 3H, CH_3); 4,00 (s, 3H, OCH_3); 4,02 (s, 3H, OCH_3); 4,21 (q, *J* = 7,20 Hz, 2H, CH_2); 7,41 (s, 1H ArH); 7,79 (s, 1H, ArH); 7,92 (s, 1H, ArH); 8,37 (s, 1H ArH); 8,80 (s, 1H ArH); 9,39 (s, 1H, NH); 11,79 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{18}Cl_2N_4O_4$, m/z : 437 $(M+H)^+$ – 439 $(M+2+H)^+$ – 441 $(M+4+H)^+$

***N*–{2,5–Dichloro–4–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}–*N'*–ethylurea (45).** (84%); white solid; Mp > 250°C. IR (ν, cm–1): 3212 (NH) – 2465 (NH^+) – 1695 (CO) – 1085 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,06 (t, *J* = 7,30 Hz, 3H, CH_3); 3,12 (q, *J* = 7,30 Hz, 2H, CH_2); 4,00 (s, 3H, OCH_3); 4,02 (s, 3H, OCH_3); 7,31 (s, 1H, NH); 7,34 (s, 1H ArH); 7,81 (s, 1H, ArH); 8,28 (s, 1H, ArH); 8,30 (s, 1H ArH); 8,50 (s, 1H ArH); 8,80 (s, 1H, NH); 11,51 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{19}Cl_2N_5O_3$, m/z : 436 $(M+H)^+$ – 438 $(M+2+H)^+$ – 440 $(M+4+H)^+$

***N*-Butyl-*N'*–{2,5–dichloro–4–[6,7–dimethoxyquinazolin–4–ylamino]phenyl}urea (46).** (49%); white solid; Mp > 250°C. IR (ν, cm–1): 3212 (NH) – 2466 (NH^+) – 1695 (CO) – 1085 (C–Cl) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,91 (t, *J* = 7,10 Hz, 3H, CH_3); 1,20-1,40 (m, 4H, CH_2CH_2); 3,08 (t, *J* = 4,60 Hz, 2H, CH_2); 4,00 (s, 3H, OCH_3); 4,02 (s, 3H, OCH_3); 7,32 (s, 1H, NH) ; 7,34 (s, 1H ArH); 7,67 (s, 1H, ArH); 8,20 (s, 1H, ArH); 8,22 (s, 1H ArH); 8,50 (s, 1H ArH); 8,80 (s, 1H, NH); 11,49 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{21}H_{23}Cl_2N_5O_3$, m/z : 464 $(M+H)^+$ – 466 $(M+2+H)^+$ – 468 $(M+4+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}acetamid chloride (47). (78%); white solid; Mp > 250°C. IR (ν, cm–1): 3213 (NH) – 2465 (NH^+) – 1640 (CO) – 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 2,03 (s, 3H, $COCH_3$) ; 2,23 (s, 3H, CH_3) ; 4,02 (s, 3H, OCH_3) ; 4,04 (s, 3H, OCH_3) ; 7,32 (s, 1H ArH) ; 7,55 (m, 3H, ArH) ; 8,21 (s, 1H ArH) ; 8,79 (s, 1H ArH) ; 9,39 (s, 1H, NH) ; 11,21 (s, 2H, NH_2^+). LC/MS ($APCI^+$) calcd for $C_{19}H_{20}N_4O_3$, m/z : 353 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}propionamid chloride (48). (87%); white solid; Mp > 250°C. IR (ν, cm–1): 3213 (NH) – 2466 (NH^+) – 1641 (CO) – 1075

(C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,06 (t, J = 7,30 Hz, 3H, CH_3); 2,21 (s, 3H, CH_3); 2,41 (q, J = 7,30 Hz, 2H, CH_2); 4,02 (s, 3H, OCH_3); 4,04 (s, 3H, OCH_3); 7,31 (s, 1H ArH); 7,52 (m, 3H, ArH); 8,28 (s, 1H ArH); 8,78 (s, 1H ArH); 9,31 (s, 1H, NH); 11,33 (s, 2H, NH_2^+). LC/MS (APCI$^+$) calcd for $C_{20}H_{22}N_4O_3$, m/z : 367 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}butanamid chloride (49). (78%); white solid; Mp > 250°C. IR (ν, cm–1): 3213 (NH) – 2465 (NH^+) – 1641 (CO) – 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,96 (t, J = 7,30 Hz, 3H, CH_3); 1,62 (m, 2H, CH_2); 2,21 (s, 3H, CH_3); 2,34 (q, J = 4,30 Hz, 2H, CH_2); 4,00 (s, 3H, OCH_3); 4,02 (s, 3H, OCH_3); 7,31 (s, 1H ArH); 7,49 (m, 3H, ArH); 8,24 (s, 1H ArH); 8,79 (s, 1H ArH); 9,32 (s, 1H, NH); 11,29 (s, 2H, NH_2^+). LC/MS (APCI$^+$) calcd for $C_{21}H_{24}N_4O_3$, m/z : 381 $(M+H)^+$

{4–[6,7–Dimethoxyquinazolin–4–ylamino]–2–methylphenyl}pentanamid chloride (50). (82%); white solid; Mp > 250°C. IR (ν, cm–1): 3213 (NH) – 2466 (NH^+) – 1642 (CO) – 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 0,92 (t, J = 7,30 Hz, 3H, CH_3); 1,32 (m, 2H, CH_2); 1,58 (m, 2H, CH_2); 2,11 (s, 3H, CH_3); 2,36 (t, J = 4,30 Hz, 2H, CH_2); 4,02 (s, 3H, OCH_3); 4,04 (s, 3H, OCH_3); 7,32 (s, 1H ArH); 7,46 (m, 3H, ArH); 8,29 (s, 1H ArH); 8,78 (s, 1H ArH); 9,32 (s, 1H, NH); 11,34 (s, 2H, NH_2^+). LC/MS (APCI$^+$) calcd for $C_{22}H_{26}N_4O_3$, m/z : 395 $(M+H)^+$

5.7 Synthesis of 4–chloroquinazoline derivatives (53-55). General procedure, spectroscopic data and melting point for compounds **53-55** were in agreement with those reported in the literature.[29]

5.8 (Allyloxy)-3-methoxybenzoic acid methyl ester (56) Potassium carbonate (22.8 g, 0.17 mole) was added to a solution of methyl vanillate (10 g, 0.06 mole) in acetone (350 mL) and was stirred for 5 min. Allyl bromide (6.1 mL, 0.07 mole) was added and the mixture was refluxed for 3 h. The inorganic solid was filtered off and the filtrate was concentrated *in vacuo*. Petroleum ether was added to the oily residue. The resulting white precipate was filtered, washed consecutively with diethyl ether and dried *in vacuo* to afford **56**.

Yield 78%; white crystals; Mp 95-97°C. IR (ν, cm–1): 1710 (CO) – 1141 (C–O–C ether) - 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 3,80 (s, 3H, OCH_3); 3,83 (s, 3H, OCH_3); 4,62 (d, J = 4,60 Hz, 2H, CH_2); 5,25-5,45 (m, 1H, CH); 6,04 (m, 1H, CH); 7,06 (d, J = 8,40 Hz, 1H, ArH); 7,45 (d, J = 2,00 Hz, 1H, ArH); 7,55 (dd, J = 2,00 Hz and J = 8,40 Hz, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_{12}H_{14}O_4$, m/z : 223 $(M+H)^+$

5.9 4-(Allyloxy)-5-methoxy-2-nitrobenzoic acid methyl ester (57). A solution of tin(IV) chloride (4.7 mL, 40 mmole) and nitric fuming acid (1.7 mL, 40 mmole) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **56** (3 g, 13.5 mmole) in CH_2Cl_2 (150 mL) cooled at –70°C. After stirring for 6 h at –70°C and cooling to room temperature, the mixture was hydrolyzed (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 70 mL), washed with a saturated potassium carbonate solution (150 mL), dried over magnesium sulfate and concentrated *in vacuo*. 2,6 g of **57** was obtained.

Yield 72%; yellow oil. IR (ν, cm–1): 1708 (CO) – 1510 (NO_2) - 1141 (C–O–C ether) - 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 3,80 (s, 3H, OCH_3); 3,93 (s, 3H, OCH_3); 4,72 (d, J = 4,60 Hz, 2H, CH_2); 5,30-5,45 (m, 1H, CH); 6,02 (m, 1H, CH); 7,32 (s, 1H, ArH); 7,65 (s, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_{12}H_{13}NO_6$, m/z : 268 $(M+H)^+$

5.10 4-Hydroxy-5-methoxy-2-nitrobenzoic acid methyl ester (58). To a solution of **57** (1 g, 3.25 mmole) dissolved in TFA (15 mL) was added dropwise Lithium perchlorate (270 mg, 2.60 mmole). After stirring for 16 h at 60°C and cooling to room temperature, the mixture was concentrated *in vacuo* and hydrolyzed (100 mL). The aqueous solution was extracted with ethyl acetate (3 x 60 mL), washed consecutively with HCl 1M (100 mL) and a saturated sodium chloride solution (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel eluting with CH_2Cl_2. Addition of petroleum ether provided the title compound as a yellow solid.

Yield 76%; yellow solid; Mp 143-145°C. IR (ν, cm–1): 3254 (OH) - 1710 (CO) – 1510 (NO_2) - 1140 (C–O–C ether) - 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 3,79 (s, 3H, OCH_3); 3,92 (s, 3H, OCH_3); 7,31 (s, 1H, ArH); 7,41 (s, 1H, ArH); 10,71 (s, 1H, OH). LC/MS (APCI$^+$) calcd for $C_9H_9NO_6$, m/z : 228 $(M+H)^+$

5.11 Generale procedure for compounds 59 and 60 by etherification of 4-hydroxy-5-methoxy-2-nitrobenzoic acid methyl ester (58).

Potassium carbonate (7.90 mmole) was added to a solution of **58** (2.65 mmole) in acetone (40 mL) and stirred 5 for min. Chloride derivative (3.96 mmole) was added and the mixture was held to reflux for 16 h. The mixture was hydrolyzed (100 mL) The aqueous solution was extracted with ethyl acetate (3 x 60 mL), washed consecutively with NaOH 1M (100 mL) and a saturated sodium chloride solution (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel eluting with CH_2Cl_2. The oily residue was dissolved in 2–propanol (2 mL) and 2–propanol saturated with HCl was added (5 mL). The resulting white precipate was filtered, washed with diethyl ether and dried *in vacuo*.

4–(2-piperidinoethoxy)–5–methoxy-2-nitrobenzoic acid methyl ester hydrochloride (59). (95%); white solid; Mp 135-137°C. IR (ν, cm–1): 2464 (NH^+) - 1710 (CO) – 1510 (NO_2) - 1141 (C–O–C ether) - 1075 (C–O–C methoxy). ^1H NMR (DMSO–d_6): δ 1,30-1,50 (m, 6H, CH_2); 2,40 (m, 4H, CH_2); 2,68 (t, J = 4,60 Hz, 2H, CH_2); 3,79 (s, 3H, OCH_3); 3,93 (s, 3H, OCH_3); 4,22 (t, J = 4,60 Hz, 2H, CH_2); 7,31 (s, 1H, ArH); 7,71 (s, 1H, ArH); 11,21 (s, 1H , NH^+). LC/MS ($APCI^+$) calcd for $C_{16}H_{22}N_2O_6$, m/z : 339 $(M+H)^+$

4–(2-morpholinoethoxy)–5–methoxy-2-nitrobenzoic acid methyl ester hydrochloride (60). (88%); white solid; Mp 151-153°C. IR (ν, cm–1): 2465 (NH^+) - 1711 (CO) – 1508 (NO_2) - 1140 (C–O–C ether) - 1075 (C–O–C methoxy). ^1H NMR (DMSO–d_6): δ 1,70-1,80 (m, 4H, CH_2); 3,31 (t, J = 4,60 Hz, 2H, CH_2); 3,50 (m, 4H, CH_2); 3,84 (s, 3H, OCH_3); 3,95 (s, 3H, OCH_3); 4,60 (t, J = 4,60 Hz, 2H, CH_2); 7,35 (s, 1H, ArH); 7,75 (s, 1H, ArH); 11,72 (s, 1H , NH^+). LC/MS ($APCI^+$) calcd for $C_{15}H_{20}N_2O_7$, m/z : 341 $(M+H)^+$

5.12 Generale procedure for compounds 61 and 62 under a hydrogen atmosphere and Raney Nickel as catalyst.

2-nitrobenzoic acid methyl ester derivatives **59** and **60** (1.50 mmole) was dissolved in a mixture dichloromethane/methanol (20 mL) and Raney nickel (100 mg) was added. The mixture was stirred under hydrogen atmosphere at room temperature for 16 h. The product was filtered through a plug of Celite before being concentrated and purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1). Addition of petroleum ether provided the title compound as a brown solid.

2-Amino-4–(2-piperidinoethoxy)–5–methoxybenzoic acid methyl ester hydrochloride (61). (92%); white solid; Mp 157-159°C. IR (ν, cm–1): 3385 (NH_2) - 2465 (NH^+) - 1710 (CO)

– 1141 (C–O–C ether) - 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,70-1,90 (m, 6H, CH_2); 3,30 (m, 4H, CH_2); 3,53 (t, J = 4,50 Hz, 2H, CH_2); 3,64 (s, 3H, OCH_3); 3,70 (s, 3H, OCH_3); 4,30 (t, J = 4,50 Hz, 2H, CH_2); 6,35 (s, 1H, ArH); 6,45 (s, 2H, NH_2); 7,13 (s, 1H, ArH); 11,30 (s, 1H , NH^+). LC/MS (APCI$^+$) calcd for $C_{15}H_{22}N_2O_4$, m/z : 309 $(M+H)^+$

2-Amino-4–(2-morpholinoethoxy)–5–methoxybenzoic acid methyl ester hydrochloride (62). (90%); white solid; Mp 172-174°C. IR (ν, cm–1): 3383 (NH_2) - 2465 (NH^+) - 1710 (CO) – 1140 (C–O–C ether) - 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,50-1,70 (m, 4H, CH_2); 3,32 (t, J = 4,60 Hz, 2H, CH_2); 3,50 (m, 4H, CH_2); 3,68 (s, 3H, OCH_3); 3,72 (s, 3H, OCH_3); 4,40 (t, J = 4,60 Hz, 2H, CH_2); 6,45 (s, 1H, ArH); 6,50 (s, 2H, NH_2); 7,13 (s, 1H, ArH); 11,72 (s, 1H , NH^+). LC/MS (APCI$^+$) calcd for $C_{15}H_{20}N_2O_7$, m/z : 311 $(M+H)^+$

5.13 2-Amino-5–methoxy-4-propoxybenzoic acid methyl ester hydrochloride (63). 4-Hydroxy-5-methoxy-2-nitrobenzoic acid methyl ester **60** (11,22 mmole) was dissolved in a mixture dichloromethane/methanol (5/5) (60 mL) and Raney nickel (100 mg) was added. The mixture was stirred under hydrogen at room temperature for 16 h. The product was filtered through a plug of Celite before being concentrated and purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1). Addition of petroleum ether provided the title compound as beige solid.

Yield (67%); beige solid; Mp 210°C. IR (ν, cm–1): 3380 (NH_2) - 2463 (NH^+) - 1708 (CO) – 1135 (C–O–C ether) - 1069 (C–O–C methoxy). ^{1}H NMR ($CDCl_3$): δ 1,10 (t, J = 7,2 Hz, 3H, CH_3); 1,95 (m, 2H, CH_2); 3,60 (s, 3H, OCH_3); 3,65 (s, 3H, OCH_3); 4,00 (t, J = 6,7 Hz, 2H, OCH_2); 5,55 (s, 2H, NH_2); 6,15 (s, 1H, ArH); 7,35 (s, 1H, ArH).

5.14 General procedure for compounds 64-66, quinazolinones derivatives.

A mixture of 2-aminoderivatives **61-63** (2.30 mmole) and ammonium formate (6.90 mmole) in formamide (3 mL) was heated at 140°C for 16 h. The reaction was hydrolysed with potassium carbonate solution (1 M, 40 mL) and extracted with ethyl acetate (5 x 30 mL). The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1).

7–(2-piperidinoethoxy)–6–methoxyquinazolin–4–one (64). (65%); white solid; Mp 150-152°C. IR (ν, cm–1): 1141 (C–O–C ether) - 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,37 (m, 2H, CH_2); 1,50 (m, 4H, CH_2); 2,39 (m, 4H, CH_2); 2,70 (t, J = 4,80 Hz, 2H, CH_2); 3,85 (s, 3H, OCH_3); 4,22 (t, J = 4,80 Hz, 2H, CH_2); 7,12 (s, 1H, ArH); 7,43 (s, 1H, ArH); 7,98 (s, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_{16}H_{21}N_3O_3$, m/z : 304 $(M+H)^+$

7–(2-morpholinoethoxy)–6–methoxyquinazolin–4–one (65). (62%); white solid; Mp 162-164°C. IR (ν, cm–1): 1140 (C–O–C ether) - 1076 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,35 (m, 4H, CH_2); 2,70 (t, J = 4,70 Hz, 2H, CH_2); 3,61 (m, 4H, CH_2); 3,87 (s, 3H, OCH_3); 4,22 (t, J = 4,70 Hz, 2H, CH_2); 7,18 (s, 1H, ArH); 7,44 (s, 1H, ArH); 8,00 (s, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_{15}H_{19}N_3O_4$, m/z : 306 $(M+H)^+$

6–Methoxy-7-propoxyquinazolin–4–one (66). (53%); beige solid; Mp >250°C. IR (ν, cm–1): 1139 (C–O–C ether) - 1071 (C–O–C methoxy). ^{1}H NMR ($CDCl_3$): δ 1,10 (t, J = 8,3 Hz, 3H, CH_3); 2,00 (m, 2H, CH_2); 4,00 (s, 3H, OCH_3); 4,25 (t, J = 8,4 Hz, 2H, CH_2); 7,20 (s, 1H, ArH); 7,65 (s, 1H, ArH); 8,05 (s, 1H, ArH); 11,50 (s, 1H, OH). LC/MS (APCI$^+$) calcd for $C_{12}H_{14}N_2O_3$, m/z : 235 $(M+H)^+$

5.14 General procedure for compounds 67-69, 4-chloroquinazolines derivatives.

A mixture of quinazolinones **64-66** (0,32 mmole) and phosphorous oxychloride (5 mL) was refluxed for 2 h. After evaporation *in vacuo*, ice water (50 mL) was added and the mixture was neutralized by ammonium hydroxide. Aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the extract was washed with a saturated aqueous sodium hydrogen carbonate solution and then dried over calcium chloride. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1) to provide a white solid.

4-Chloro-7–(2-piperidinoethoxy)–6–methoxyquinazoline (67). (77%); white solid; Mp 191-193°C. IR (ν, cm–1): 1141 (C–O–C ether) - 1086 (C–Cl) - 1075 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,38 (m, 2H, CH_2); 1,50 (m, 4H, CH_2); 2,41 (m, 4H, CH_2); 2,72 (t, J = 4,80 Hz, 2H, CH_2); 3,98 (s, 3H, OCH_3); 4,31 (t, J = 4,80 Hz, 2H, CH_2); 7,33 (s, 1H, ArH); 7,45 (s, 1H, ArH); 8,85 (s, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_{16}H_{20}ClN_3O_2$, m/z : 322 $(M+H)^+$ - 324 $(M+2+H)^+$

4-Chloro-7–(2-morpholinoethoxy)–6–methoxyquinazoline (68). (70%); white solid; Mp 195-197°C. IR (ν, cm–1): 1141 (C–O–C ether) - 1086 (C–Cl) - 1077 (C–O–C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,45 (m, 4H, CH_2); 2,77 (t, J = 4,70 Hz, 2H, CH_2); 3,57 (m, 4H, CH_2); 3,99 (s, 3H, OCH_3); 4,32 (t, J = 4,70 Hz, 2H, CH_2); 7,35 (s, 1H, ArH); 7,46 (s, 1H, ArH); 8,87 (s, 1H, ArH). LC/MS (APCI$^+$) calcd for $C_{15}H_{18}ClN_3O_3$, m/z : 324 $(M+H)^+$ - 326 $(M+2+H)^+$

4-Chloro-6–methoxy-7-propoxyquinazoline (69). (62%); beige solid; Mp 162-164°C. IR (ν, cm–1): 1138 (C–O–C ether) - 1080 (C–Cl) - 1076 (C–O–C methoxy). ^{1}H NMR ($CDCl_3$): δ 1,20 (t, J = 8,1 Hz, 3H, CH_3); 2,10 (m, 2H, CH_2); 4,00 (s, 3H, CH_3); 4,15 (t, J = 8,1 Hz, 2H,

CH_2); 7,20 (s, 1H, ArH); 7,50 (s, 1H, ArH); 8,30 (s, 1H, ArH). LC/MS ($APCI^+$) calcd for $C_{12}H_{13}ClN_2O_2$, m/z : 253 $(M+H)^+$ - 255 $(M+2+H)^+$

5.15 General procedure for compounds 70–80 by nucleophilic substitution of 4–chloroquinazoline derivatives (53-55, 67-69).

The 4–chloroquinazoline derivatives (0,1 g) was added dropwise to a solution of the synthesized aniline **10** or **14** (2 eq.) and NaH (60% in oil) (3 eq.) in DMF (3 mL). The reaction was held at 60°C for 1 h. After concentration *in vacuo*, the product was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1). The oily residue was dissolved in 2–propanol (2 mL) and 2–propanol saturated with HCl was added (5 mL). The resulting precipate was filtered, washed with diethyl ether and dried *in vacuo*.

{4-[7-(2-Diethylaminoethoxy)-6-methoxyquinazolin-4-ylamino]-2-methylphenyl}carbamic acid methyl ester dichloride (70). (37%); white solid; Mp 244-246°C. IR (ν, cm–1): 3211 (NH) - 2465 (NH^+) - 1711 (CO) - 1265 (N-CO-O) - 1141 (C-O-C ether) - 1076 (C-O-C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,20-1,30 (m, 9H, CH_3); 2,20 (s, 3H, CH_3); 3,22 (q, J = 7,10 Hz, 4H, CH_2); 3,61 (t, J = 4,20 Hz, 2H, CH_2); 4,00 (s, 3H, OCH_3); 4,12 (t, J = 7,00 Hz, 2H, CH_2); 4,61 (t, J = 4,20 Hz, 2H, CH_2); 7,40-7,50 (m, 4H, ArH); 8,51 (s, 1H, ArH); 8,75 (s, 1H, ArH); 8,95 (s, 1H, NH); 10,95 (s, 2H, NH_2^+); 11,78 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{25}H_{33}N_5O_4$, m/z : 468 $(M+H)^+$

{4-[6-(2-Diethylaminoethoxy)-7-methoxyquinazolin-4-ylamino]-2-methylphenyl}carbamic acid methyl ester dichloride (71). (35%); white solid; Mp 230-232°C. IR (ν, cm–1): 3212 (NH) - 2465 (NH^+) - 1710 (CO) - 1266 (N-CO-O) - 1141 (C-O-C ether) - 1076 (C-O-C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,30-1,40 (m, 9H, CH_3); 2,20 (s, 3H,

CH_3); 3,31 (q, *J* = 7,10 Hz, 4H, CH_2); 3,61 (t, *J* = 4,20 Hz, 2H, CH_2); 3,96 (s, 3H, OCH_3); 4,12 (t, *J* = 7,00 Hz, 2H, CH_2); 4,62 (t, *J* = 4,20 Hz, 2H, CH_2); 7,22 (s, 1H, ArH); 7,31 (d, *J* = 8,10 Hz, 2H, ArH); 7,60 (m, 2H, ArH); 8,22 (s, 1H, ArH); 8,51 (s, 1H, ArH); 8,78 (s, 1H, NH); 10,04 (s, 2H, NH_2^+); 10,63 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{25}H_{33}N_5O_4$, m/z : 468 $(M+H)^+$

{4-[6-Methoxy-7-(2-piperidinoethoxy)quinazolin-4-ylamino]-2-methylphenyl}carbamic acid ethyl ester dichloride (72). (31%); yellow solid; Mp 240-242°C. IR (ν, cm–1): 3212 (NH) - 2465 (NH^+) - 1710 (CO) - 1265 (N-CO-O) - 1142 (C-O-C ether) - 1076 (C-O-C methoxy). ^1H NMR (DMSO–d_6): δ 1,22 (t, *J* = 7,00 Hz, 3H, CH_3); 1,60-1,80 (m, 4H, CH_2); 2,20 (s, 3H, CH_3); 3,05 (t, *J* = 4,20 Hz, 2H, CH_2); 3,30-3,50 (m, 6H, CH_2); 3,96 (s, 3H, OCH_3); 4,12 (q, *J* = 7,00 Hz, 2H, CH_2); 4,68 (t, *J* = 4,20 Hz, 2H, CH_2); 7,40-7,50 (m, 4H, ArH); 8,50 (s, 1H, ArH); 8,80 (s, 1H, ArH); 8,85 (s, 1H, NH); 10,96 (s, 2H, NH_2^+); 11,65 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{26}H_{33}N_5O_4$, m/z : 480 $(M+H)^+$

{4-[6-Methoxy-7-(2-morpholinoethoxy)quinazolin-4-ylamino]-2-methylphenyl}carbamic acid ethyl ester dichloride (73). (29%); yellow solid; Mp 235-237°C. IR (ν, cm–1): 3210 (NH) - 2465 (NH^+) - 1710 (CO) - 1265 (N-CO-O) - 1141 (C-O-C ether) - 1076 (C-O-C methoxy). ^1H NMR (DMSO–d_6): δ 1,24 (t, *J* = 7,00 Hz, 3H, CH_3); 1,40-1,50 (m, 4H, CH_2); 2,21 (s, 3H, CH_3); 3,06 (t, *J* = 4,30 Hz, 2H, CH_2); 3,20-3,40 (m, 4H, CH_2); 4,01 (s, 3H, OCH_3); 4,12 (q, *J* = 7,00 Hz, 2H, CH_2); 4,69 (t, *J* = 4,30 Hz, 2H, CH_2); 7,40-7,60 (m, 4H, ArH) ; 8,48 (s, 1H, ArH); 8,78 (s, 1H, ArH); 8,93 (s, 1H, NH); 10,87 (s, 2H, NH_2^+); 11,61 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{25}H_{31}N_5O_5$, m/z : 482 $(M+H)^+$

{4-[6-methoxy-7-propyloxyquinazolin-4-ylamino]-2-methylphenyl}carbamic acid ethyl ester dichloride (74). (45%); yellow solid; Mp >250°C. IR (ν, cm–1): 3205 (NH) - 2460 (NH^+) - 1712 (CO) - 1270 (N-CO-O) - 1145 (C-O-C ether) - 1076 (C-O-C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,00 (t, *J* = 7,3 Hz, 3H, CH_3); 1,30 (t, *J* = 7,0 Hz, 3H, CH_3); 1,90 (q, *J* = 6,7 Hz, 2H, CH_2); 2,30 (s, 3H, CH_3); 3,95 (s, 3H, CH_3); 4,15 (m, 4H, $2CH_2$); 7,30 (m, 1H, ArH); 7,35 (m, 2H, 2ArH); 7,50 (s, 1H, ArH); 8,10 (s, 1H, ArH); 8,60 (s, 1H, NH); 8,90 (s, 1H, ArH); 10,65 (s, 1H, NH). LC/MS ($APCI^+$) calcd for $C_{22}H_{26}N_4O_4$, m/z : 411 $(M+H)^+$

4-[6-Butoxy-7-(2-diethylaminoethoxy)quinazolin-4-ylamino]-2-methylphenyl}carbamic acid ethyl ester dichloride (75). (31%); white solid; Mp > 250°C. IR (ν, cm–1): 3211 (NH) - 2465 (NH^+) - 1710 (CO) - 1265 (N-CO-O) - 1141 (C-O-C ether). ^{1}H NMR (DMSO–d_6): δ 1,00-1,15 (m, 9H, CH_3); 1,21 (t, *J* = 7,00 Hz, 3H, CH_3); 1,40-1,50 (m, 4H, CH_2); 1,50 (m, 2H, CH_2); 1,78 (m, 2H, CH_2); 2,21 (s, 3H, CH_3); 2,62 (q, *J* = 7,20 Hz, 2H, CH_2); 2,91 (t, *J* = 4,20 Hz, 2H, CH_2); 4,10-4,20 (m, 6H, CH_2); 7,11 (s, 1H, ArH); 7,32 (d, *J* = 8,40 Hz, 1H, ArH); 7,57 (d, *J* = 2,10 Hz, 1H, ArH); 7,60 (dd, *J* = 2,10 Hz and 8,40 Hz, 1H, ArH); 7,81 (s, 1H, ArH); 8,42 (s, 1H, ArH); 8,73 (s, 1H, NH); 10,37 (s, 2H, NH_2^+); 11,44 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{28}H_{39}N_5O_4$, m/z : 510 $(M+H)^+$

{2-Chloro-4-[7-(2-diethylaminoethoxy)-6-methoxyquinazolin-4-ylamino]phenyl}carbamic acid methyl ester dichloride (76). (29%); yellow crystals; Mp > 250°C. IR (ν, cm–1): 3212 (NH) - 2465 (NH^+) - 1712 (CO) - 1265 (N-CO-O) - 1141 (C-O-C ether) - 1085 (C-Cl) - 1076 (C-O-C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,05 (t, *J* = 7,10 Hz, 6H, CH_3); 1,22 (t, *J* = 7,00 Hz, 3H, CH_3); 3,20 (q, *J* = 7,10 Hz, 4H, CH_2); 3,52 (t, *J* = 4,30 Hz, 2H, CH_2); 4,00 (s, 3H, OCH_3); 4,10 (q, *J* = 7,00 Hz, 2H, CH_2); 4,55 (t, *J* = 4,30 Hz, 2H, CH_2); 7,21 (s, 1H, ArH); 7,51 (d, *J* = 8,10 Hz, 1H, ArH); 7,72 (dd, *J* = 2,30 Hz and 8,10 Hz, 1H,

ArH); 7,83 (s, 1H, ArH); 8,11 (d, *J* = 2,30 Hz, 1H, ArH); 8,51 (s, 1H, ArH); 9,02 (s, 1H, NH); 9,65 (s, 2H, NH_2^+); 11,39 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{24}H_{30}ClN_5O_4$, m/z : 488 $(M+H)^+$ - 490 $(M+2+H)^+$

{2-Chloro-4-[6-methoxy-7-(2-piperidinoethoxy)quinazolin-4-ylamino]phenyl}carbamic acid ethyl ester dichloride (77). (29%); yellow solid; Mp 213-215°C. IR (ν, cm–1): 3212 (NH) - 2465 (NH^+) - 1711 (CO) - 1265 (N-CO-O) - 1140 (C-O-C ether) - 1085 (C-Cl) - 1076 (C-O-C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,21 (t, *J* = 7,00 Hz, 3H, CH_3); 1,70-1,85 (m, 4H, CH_2); 3,22 (t, *J* = 4,40 Hz, 2H, CH_2); 3,30-3,50 (m, 6H, CH_2); 4,01 (s, 3H, OCH_3); 4,10 (q, *J* = 7,00 Hz, 2H, CH_2); 4,67 (t, *J* = 4,40 Hz, 2H, CH_2); 7,35-7,50 (m, 4H, ArH); 8,52 (s, 1H, ArH); 8,81 (s, 1H, ArH); 8,84 (s, 1H, NH); 10,85 (s, 2H, NH_2^+); 11,51 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{25}H_{30}ClN_5O_4$, m/z : 500 $(M+H)^+$ - 502 $(M+2+H)^+$

{2-Chloro-4-[6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-ylamino]phenyl}carbamic acid ethyl ester dichloride (78). (32%); yellow solid; Mp 221-223°C. IR (ν, cm–1): 3210 (NH) - 2465 (NH^+) - 1710 (CO) - 1265 (N-CO-O) - 1141 (C-O-C ether) - 1085 (C-Cl) - 1076 (C-O-C methoxy). ^{1}H NMR (DMSO–d_6): δ 1,23 (t, *J* = 7,10 Hz, 3H, CH_3); 1,60-1,70 (m, 4H, CH_2); 3,54 (t, *J* = 4,40 Hz, 2H, CH_2); 3,70-3,90 (m, 4H, CH_2); 4,01 (s, 3H, OCH_3); 4,10 (q, *J* = 7,10 Hz, 2H, CH_2); 4,68 (t, *J* = 4,40 Hz, 2H, CH_2); 7,41 (s, 1H, ArH); 7,60-7,70 (m, 2H, ArH); 8,00 (s, 1H, ArH); 8,52 (s, 1H, ArH); 8,86 (s, 1H, ArH); 9,12 (s, 1H, NH); 10,87 (s, 2H, NH_2^+); 11,71 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{24}H_{28}ClN_5O_5$, m/z : 502 $(M+H)^+$ - 504 $(M+2+H)^+$

{2-Chloro-4-[6-methoxy-7-propyloxyquinazolin-4-ylamino]phenyl}carbamic acid ethyl ester dichloride (79). (49%); yellow solid; Mp >250°C. IR (ν, cm–1): 3206 (NH) - 2455

(NH^+) - 1715 (CO) - 1259 (N-CO-O) - 1120 (C-O-C ether) – 1089 (C-O-C methoxy). ^1H NMR (DMSO–d_6): δ 1,00 (t, *J* = 7,2 Hz, 3H, CH_3); 1,30 (t, *J* = 7,3 Hz, 3H, CH_3); 1,85 (q, *J* = 6,7 Hz, 2H, CH_2); 4,00 (s, 3H, CH_3); 4,15 (m, 4H, $2CH_2$); 7,25 (s, 1H, ArH); 7,75 (m, 2H, 2ArH); 7,95 (s, 1H, ArH); 8,40 (s, 1H, NH); 8,95 (s, 1H, ArH); 9,10 (s, 1H, ArH); 11,40 (s, 1H, NH). LC/MS ($APCI^+$) calcd for $C_{21}H_{23}ClN_4O_4$, m/z : 431 $(M+H)^+$ - 433 $(M+2+H)^+$

{4-[6-Butoxy-7-(2-diethylaminoethoxy)quinazolin-4-ylamino]-2-chlorophenyl}carbamic acid ethyl ester dichloride (80). (30%); yellow solid; Mp 189-191°C. IR (ν, cm–1): 3211 (NH) - 2465 (NH^+) - 1710 (CO) - 1265 (N-CO-O) - 1141 (C-O-C ether) – 1085 (C-Cl). ^1H NMR (DMSO–d_6): δ 0,98 (t, *J* = 6,90 Hz, 3H, CH_3); 1,20-1,30 (m, 9H, CH_3); 1,50 (m, 2H, CH_2); 1,78 (m, 2H, CH_2); 3,31 (t, *J* = 4,20 Hz, 2H, CH_2); 3,64 (t, *J* = 7,20 Hz, 2H, CH_2); 4,11 (q, *J* = 6,90 Hz, 2H, CH_2); 4,61 (t, *J* = 6,00 Hz, 2H, CH_2); 7,42 (s, 1H, ArH); 7,50 (d, *J* = 8,20 Hz, 1H, ArH); 7,76 (dd, *J* = 2,00 Hz and 8,20 Hz, 1H, ArH); 7,98 (d, *J* = 2,00 Hz, 1H, ArH); 8,42 (s, 1H, ArH); 8,83 (s, 1H, ArH); 9,12 (s, 1H, NH); 10,71 (s, 2H, NH_2^+); 11,35 (s, 1H, NH^+). LC/MS ($APCI^+$) calcd for $C_{27}H_{36}ClN_5O_4$, m/z : 530 $(M+H)^+$ - 532 $(M+2+H)^+$

Pharmacology

Cell Culture and Cell Proliferation Assays. Human prostate cancer cells PC3 and breast cancer cell line MCF-7 were grown at 37°C in a humidified atmosphere containing 5 % CO_2, respectively in RPMI–1640 (Sigma) and MEM (Sigma) supplemented with 10 % fetal bovine serum, glutamine (2 mM), penicillin (100 IU/mL), and streptomycin (100 µg/mL). HT29 colon cancer cells and EAHY926, immortalized umbilical immortalized cancer cell lines were grown at 37°C in a humidified atmosphere containing 5 % CO_2 in DMEM + Glutamax–I (Gibco) supplemented with 10 % fetal bovine serum, penicillin (100 IU/mL), and streptomycin (100 µg/mL)

In the cell proliferation assay, cells were plated in triplicate on 96–well plates (3.000 cells per well) and incubated for 24 h. Cells were then incubated in culture medium that contained various concentrations of tested compounds, each dissolved in less than 0.1 % DMSO. After 72 h, cell growth was estimated by the colorimetric MTS test.

In Vitro Kinase Assays. Kinase assays were performed in 96–well plates (Multiscreen Durapore, Millipore) using [γ–32P]ATP (Amersham Biosciences) and the synthetic polymer poly(Glu4/Tyr) (Sigma Chemicals) as a phosphoacceptor substrate. Tested compounds were dissolved in DMSO, final concentration of DMSO in assay solutions was 0,1 %, which was shown to have no effect on kinase activity.

EGFR Tyrosine Kinase Activity: 20 ng of EGFR (purified from human carcinoma A431 cells, Sigma Chemicals) were incubated for 1 h at 28 °C using various concentrations of tested compounds in kinase buffer (HEPES 50 mM pH 7.5, BSA 0.1 mg/mL, MnCl2 10 mM, MgCl2 5 mM, Na3VO4 100 μM, DTT 0.5 mM, poly(Glu4/Tyr) 250 μg/mL, ATP 5 μM, [γ–32P]ATP 0.5 μCi).

VEGFR–2 Tyrosine kinase Activity: 10 ng of VEGFR–2 (Recombinant Human Protein, Invitrogen) were incubated for 1 h at 28°C using various concentrations of tested compounds in kinase buffer (Tris 50mM pH 7.5, BSA 25μg/mL, MnCl2 1.5 mM, MgCl2 10 mM, DTT 2.5 mM, Na3VO4 100 μM, β–Glycerophosphate 5 mM, poly(Glu4/Tyr) 250 μg/mL, ATP 5 μM, [γ–32P]ATP 0.5 μCi).

The reaction was stopped by adding 20 μL of trichloroacetic acid (100 %). Wells were screened out and washed 10 times with trichloroacetic acid (10 % aqueous solution). Plates were counted in a Top Count for 1 min per well.

Molecular Modelling

All the calculations were carried out under the Sybyl 6.9.1 molecular modelling package running on Silicon Graphics Octane 2 workstations. The ligands were built from the internal fragments library of Sybyl and their geometry was optimized by the Powell method available in the Maximin2 procedure to a gradient of 0.001 Kcal/mol.Å. The dielectric constant was set to 4 to implicitly represent a biological medium, the atomic charges were attributed following the Gasteiger–Hückel method and the energy minimization was run with the Tripos force field. The structure of the protein cocrystallized with an inhibitor was obtained from the Protein Data Bank (http://www.pdb.org) under the entries 1M17 and 1YWN for EGFR and VEGFR–2, respectively.