Regioselective Synthesis and Biological Evaluation of *N*-Substituted 2-Aminoquinazolin-4-ones

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Experimental section

General information

The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift for the hydrogen residue peak and carbon-13 peak in the deuterated solvent, $CDCl_3$, or DMSO-d_6.[1] The coupling constant (*J*) values are expressed in hertz (Hz). The numbers of protons directly attached to the individual carbons were determined by ^{13}C NMR DEPT experiments. Thin-layer chromatography (TLC) was performed on silica gel plates. Compounds on TLC were visualized by illumination under UV light (254 nm), or dipped into 10% phosphomolybdic acid in ethanol followed by charring on a hot plate. Solvent systems are expressed as a volumetric ratio (*v/v*) of the less polar component to the more polar component. Silica gel (230-400 mesh) was used for flash column chromatography and this technique has been described by W. C. Still *et al.*[2] Evaporations were carried out under reduced pressure (water aspirator or vacuum pump) with the bath temperature below 50 ^oC unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

General procedure for cytotoxicity assay (Table 2)

Leukemia cell line HL-60 was obtained from ATCC. HL-60 was cultivated in RPMI 1640 media (Mediatech, Inc. Manassas, VA, USA) containing 10% fetal calf serum, 100 unit/mL penicillin, 100 mg/mL streptomycin, and 2 mM glutamine in a 5% CO_2 incubator at 37 ^oC. Cytotoxicity was measured by MTT assay after continuous treatment with the tested compounds for 4 days as described. The quantitative results of IC_{50} were estimated with the 3 replicates data.[3]

[General procedure 1] Preparation of 3-substituted 2-aminoquinazolin-4-one (3) under the optimized *p*-TsOH condition (Scheme 2)

To a mixture of *N*-substituted cyanamide[4] (**2**, 1.5 equiv) and methyl anthranilate (**1**, 1.0 equiv) in *tert*-butanol (0.5 M) was added *p*-toluenesulfonic acid monohydrate (1.2 equiv). The mixture was heated at reflux temperature for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ and 2 N NaOH aqueous solution. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 3-substituted 2-aminoquinazolin-4-one (**3**). An analytical sample of 3-substituted 2-aminoquinazolin-4-one (**3**) was obtained by re-

crystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)). The regioisomer, 2-(*N*-substituted-amino)quinazolin-4-one (**4**), was retrieved by acidifying the aqueous layer with 2 N aqueous acetic acid solution (0.8 equiv to the 2 N NaOH aqueous solution) followed by $CHCl_3$ extraction. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**).

2-Amino-3-phenylquinazolin-4-one[5,6] **(3aa)**

Compound **3aa** was prepared by *general procedure 1*. The product (**3aa**, solid, 0.6201 g, 2.614 mmol, 64%, R_f = 0.20 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 245–250 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.89 (d, 1H, *J* = 8.0 Hz), 7.62–7.50 (m, 4H), 7.35 (d, 2H, *J* = 7.5 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 6.27 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.3, 152.1, 150.6, 135.9, 134.9 (CH), 130.4 (CH), 129.6 (CH), 129.3 (CH), 127.0 (CH), 124.4 (CH), 122.0 (CH), 117.3; MS (EI, 70 eV) *m/z* 77 (22), 237 (100) (M^+); HRMS (APCI, TOF) calcd for $C_{14}H_{12}N_3O$: 238.0980 (M+H). Found: 238.0986.

2-Amino-3-(4-tolyl)quinazolin-4-one[7] **(3ab)**

Compound **3ab** was prepared by *general procedure 1* or *general procedure 3*. The product (**3ab**, solid, 0.1471 g, 0.586 mmol, 76%, R_f = 0.35 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 266 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.88 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.60 (dt, 1H, *J* = 7.2, 1.6 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.25–7.21 (m, 3H), 7.10 (dt, 1H, *J* = 8.0, 0.8 Hz), 6.23 (br, 2H, NH_2), 2.40 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.9, 151.8, 150.1, 138.5, 134.3 (CH), 132.8, 130.5 (CH), 128.5 (CH), 126.5 (CH), 123.9 (CH), 121.4 (CH), 116.8, 20.8 (CH_3); MS (EI, 70 eV) *m/z* 90 (19), 251 (100) (M^+); HRMS (APCI, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1132.

2-Amino-3-(4-methoxyphenyl)quinazolin-4-one[6] **(3ac)**

Compound **3ac** was prepared by *general procedure 1*. The product (**3ac**, solid, 1.0113 g, 3.748 mmol, 84%, R_f = 0.20 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 226–228 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.89 (dd, 1H, *J* = 7.8, 1.0 Hz), 7.59 (dt, 1H, *J* = 7.7, 1.6 Hz), 7.27–7.23 (m, 3H), 7.12–7.09 (m, 3H), 6.27 (br, 2H, NH_2), 3.83 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.5, 160.0, 152.5, 150.6, 134.8 (CH), 130.4 (CH), 128.3, 127.0 (CH), 124.3 (CH), 121.9 (CH), 117.3, 115.6 (CH), 55.8 (CH_3); MS (EI, 70 eV) *m/z* 90 (20), 145 (45), 252 (29), 267 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{15}H_{14}N_3O_2$: 268.1086 (M+H). Found: 268.1083.

2-Amino-3-(4-chlorophenyl)quinazolin-4-one (3ad)

Compound **3ad** was prepared by *general procedure 1*. The product (**3ad**, solid, 1.0113 g, 1.229 mmol, 38%, R_f = 0.25 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 252–257 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.88 (dd, 1H, *J* = 7.8, 0.8 Hz), 7.62 (d, 2H, *J* = 8.5 Hz), 7.59 (t, 1H, *J* = 8.1 Hz), 7.40 (d, 2H, *J* = 8.6 Hz), 7.24 (d, 1H, *J* = 8.2 Hz), 7.11 (t, 1H, *J* = 7.7 Hz), 6.41 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.3, 152.0, 150.7, 134.93 (CH), 134.90, 134.3, 131.4 (CH), 130.5 (CH), 127.0 (CH), 124.4

(CH), 121.9 (CH), 117.1; MS (EI, 70 eV) *m/z* 271 (100) (M^+), 273 (47) (M+2); HRMS (ESI^+, TOF) calcd for $C_{14}H_{11}ClN_3O$: 272.0591 (M+H). Found: 272.0588.

2-Amino-3-(4-nitrophenyl)quinazolin-4-one (3ae)

Compound **3ae** was prepared by *general procedure 1*. The product (**3ae**, solid, 0.2248 g, 0.841 mmol, 25%, R_f = 0.23 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 267–274 ^oC ($CHCl_3$ / EtOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 8.40 (d, 2H, *J* = 9.0 Hz), 7.90 (d, 1H, *J* = 7.5 Hz), 7.71 (d, 2H, *J* = 8.5 Hz), 7.63 (dt, 1H, *J* = 7.8, 1.0 Hz), 7.25 (d, 1H, *J* = 8.5 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 6.50 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.7, 150.9, 150.3, 147.9, 141.6, 134.6 (CH), 130.9 (CH), 126.5 (CH), 125.2 (CH), 124.0 (CH), 121.6 (CH), 116.5; MS (EI, 20 eV) *m/z* 108 (33), 138 (52), 181 (25), 281 (60), 282 (100) (M^+); HRMS (EI, sector) calcd for $C_{14}H_{10}N_4O_3$: 282.0753. Found: 282.0744.

2-Amino-3-(2-tolyl)quinazolin-4-one[6] (3af)

Compound **3af** was prepared by *general procedure 1*. The product (**3af**, solid, 1.3920 g, 5.539 mmol, 71%, R_f = 0.38 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 199–201 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.90 (d, 1H, *J* = 7.5 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), 7.46–7.37 (m, 3H), 7.26 (d, 2H, *J* = 8.0 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 6.30 (br, 2H, NH_2), 2.04 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.4, 151.4, 150.3, 135.8, 134.5, 134.4 (CH), 131.3 (CH), 129.5 (CH), 128.8 (CH), 127.7 (CH), 126.6 (CH), 124.0 (CH), 121.6 (CH), 116.6, 16.8 (CH_3); MS (ESI^+) *m/z* 252 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1127.

2-Amino-3-propylquinazolin-4-one[6] (3ah)

Compound **3ah** was prepared by *general procedure 1*. The product (**3ah**, solid, 0.2586 g, 1.273 mmol, 19%, R_f = 0.15 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 182–184 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.87 (d, 1H, *J* = 8.0 Hz), 7.53 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 7.06 (t, 1H, *J* = 7.0 Hz), 6.97 (br, 2H, NH_2), 3.92 (t, 2H, *J* = 7.5 Hz, CH_2), 1.62-1.55 (m, 2H, CH_2), 0.87 (t, 3H, *J* = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.3, 152.2, 149.8, 134.5 (CH), 126.8 (CH), 123.9 (CH), 121.9 (CH), 116.4, 42.9 (CH_2), 20.7 (CH_2), 11.2 (CH_3); MS (ESI^+) *m/z* 204 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{11}H_{14}N_3O$: 204.1137 (M+H). Found: 204.1115.

2-Amino-3-(2-bromophenyl)quinazolin-4-one (3ai)

Compound **3ai** was prepared by *general procedure 1*. The product (**3ai**, solid, 0.9679 g, 3.06 mmol, 87%, R_f = 0.30 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 237–238 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.89 (dd, 1H, *J* = 7.9, 1.4 Hz), 7.85 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.62 (dt, 1H, *J* = 7.8, 1.6 Hz), 7.60–7.51 (m, 2H), 7.46 (dt, 1H, *J* = 7.8, 2.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 8.0 Hz), 6.44 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 151.4, 150.8, 135.08 (CH), 135.06, 134.1 (CH), 131.7 (CH), 131.6 (CH), 130.0 (CH), 127.0 (CH), 124.4 (CH), 123.2, 122.0 (CH), 116.9; MS (EI, 20 eV) *m/z* 236 (100), 315 (22) (M^+), 317 (20) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{10}BrN_3O$: 315.0007. Found: 315.0000.

2-Amino-3-(2-bromo-4-methylphenyl)quinazolin-4-one (3aj)

Compound **3aj** was prepared by *general procedure 1*. The product (**3aj**, solid, 0.3509 g, 1.06 mmol, 53%, R_f = 0.25 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 293–294 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.88 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.68 (s, 1H), 7.61 (t, 1H, *J* = 8.4 Hz), 7.38 (s, 2H), 7.24 (d, 1H, *J* = 8.0 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), 6.42 (br, 2H, NH_2), 2.40 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.7, 151.6, 150.8, 141.7, 135.0 (CH), 134.3 (CH), 132.4, 131.0 (CH), 130.6 (CH), 127.0 (CH), 124.4 (CH), 122.8, 121.9 (CH), 116.9, 20.9 (CH_3); MS (EI, 20 eV) *m/z* 250 (100), 329 (17) (M^+), 331 (16) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}BrN_3O$: 329.0164. Found: 329.0165.

2-Amino-3-(2-bromo-4-fluorophenyl)quinazolin-4-one (3ak)

Compound **3ak** was prepared by *general procedure 1*. The product (**3ak**, white solid, 0.8447 g, 2.53 mmol, 84%, R_f = 0.11 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 303–304 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.89 (d, 1H, *J* = 8.0 Hz), 7.84 (dd, 1H, *J* = 8.4, 2.4 Hz), 7.64–7.60 (m, 2H), 7.45 (dt, 1H, *J* = 8.4, 2.4 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 7.4 Hz), 6.57 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.6 (d, *J* = 248 Hz), 161.7, 151.5, 150.8, 135.1 (CH), 133.1 (d, *J* = 10.0 Hz, CH), 131.8 (d, *J* = 3.0 Hz), 127.0 (CH), 124.4 (CH), 124.2 (d, *J* = 11.0 Hz), 122.0 (CH), 121.3 (d, *J* = 26.0 Hz, CH), 117.0 (d, *J* = 23.0 Hz, CH), 116.8; ^{19}F NMR (DMSO-d_6, 375 MHz) δ -110.4; MS (EI, 20 eV) *m/z* 254 (100), 333 (22) (M^+), 335 (22) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{19}BrFN_3O$: 332.9914. Found: 332.9915.

2-Amino-6-chloro-3-phenylquinazolin-4-one (3ba)

Compound **3ba** was prepared by *general procedure 1*. The product (**3ba**, solid, 0.9203 g, 3.387 mmol, 53%, R_f = 0.35 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 240 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.80 (d, 1H, *J* = 2.5 Hz), 7.61 (dd, 1H, *J* = 9.0, 2.0 Hz), 7.57 (t, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 7.5 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 9.0 Hz), 6.44 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.9, 152.0, 149.0, 135.1, 134.4 (CH), 130.0 (CH), 129.3 (CH), 128.7 (CH), 126.1 (CH), 125.2 (CH), 125.2, 117.8; MS (EI, 70 eV) *m/z* 271 (100) (M^+), 273 (30) (M+2); HRMS (ESI^+, TOF) calcd for $C_{14}H_{10}ClN_3O$: 272.0591 (M+H). Found: 272.0587; Anal. calcd for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.71; N, 15.47. Found: C, 62.21; H, 3.95; N, 15.07.

2-Amino-6-chloro-3-(4-tolyl)quinazolin-4-one (3bb)

Compound **3bb** was prepared by *general procedure 1* or *general procedure 3*. The product (**3bb**, solid, 0.6341 g, 2.219 mmol, 68%, R_f = 0.33 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 315 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.80 (d, 1H, *J* = 2.5 Hz), 7.61 (dd, 1H, *J* = 8.8, 2.5 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.23 (d, 2H, *J* = 8.1 Hz), 6.42 (br, 2H, NH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.5, 152.7, 149.5, 139.2, 134.8 (CH), 133.0, 131.0 (CH), 128.9 (CH), 126.6 (CH), 125.7 (CH), 125.6, 118.2, 21.3 (CH_3); MS (EI, 70 eV) *m/z* 123 (18), 285 (100) (M^+), 287 (23) (M+2); HRMS (APCI, TOF) calcd for $C_{15}H_{13}ClN_3O$: 286.0747 (M+H). Found: 286.0742.

2-Amino-6-chloro-3-(4-methoxyphenyl)quinazolin-4-one (3bc)

Compound **3bc** was prepared by *general procedure 1*. The product (**3bc**, solid, 1.1063 g, 3.666 mmol, 66%, R_f = 0.25 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 300–305 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.80 (d, 1H, *J* = 2.7 Hz), 7.60 (dd, 1H, *J* = 8.7, 2.3 Hz), 7.27 (d, 2H, *J* = 9.1 Hz), 7.24 (d, 1H, *J* = 9.5 Hz), 7.09 (d, 2H, *J* = 8.7 Hz), 6.44 (br, 2H, NH_2), 3.82 (s, 3H, OMe); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 160.1, 152.9, 149.5, 134.8 (CH), 130.3 (CH), 128.0, 126.5 (CH), 125.7 (CH), 125.5, 118.3, 115.7 (CH), 55.9 (CH_3); MS (EI, 70 eV) *m/z* 124 (24), 179 (20), 286 (41), 301 (100) (M^+), 303 (42) (M+2); HRMS (ESI^+, TOF) calcd for $C_{15}H_{13}ClN_3O_2$: 302.0696 (M+H). Found: 302.0697.

2-Amino-6-chloro-3-(4-nitrophenyl)quinazolin-4-one (3be)

Compound **3be** was prepared by *general procedure 1*, except the solvent was replaced by 2-methyl-2-butanol, and the reaction time was extended to 12 h. The product (**3be**, solid, 0.2900 g, 0.961 mmol, 22%, R_f = 0.23 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. > 320 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.42 (d, 2H, *J* = 9.0 Hz), 7.82 (d, 1H, *J* = 3.0 Hz), 7.74 (d, 2H, *J* = 9.0 Hz), 7.64 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.27 (d, 1H, *J* = 9.0 Hz), 6.66 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.8, 151.4, 149.1, 148.0, 141.3, 134.6 (CH), 130.9 (CH), 126.2 (CH), 125.26, 125.24 (CH), 125.22 (CH), 117.6; MS (ESI^+) *m/z* 317 (100) (M+H), 319 (30) (M+H+2); HRMS (ESI^+, TOF) calcd for $C_{14}H_{10}ClN_4O_3$: 317.0441 (M+H). Found: 317.0421.

2-Amino-6-chloro-3-(2-tolyl)quinazolin-4-one (3bf)

Compound **3bf** was prepared by *general procedure 1*. The product (**3bf**, solid, 0.7711 g, 2.699 mmol, 54%, R_f = 0.43 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 200–203 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.82 (d, 1H, *J* = 2.5 Hz), 7.63 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.46–7.37 (m, 3H), 7.27 (d, 2H, *J* = 8.5 Hz), 6.45 (br, 2H, NH_2), 2.03 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.4, 151.7, 149.1, 135.7, 134.5 (CH), 134.1, 131.4 (CH), 129.6 (CH), 128.7 (CH), 127.7 (CH), 126.2 (CH), 125.30 (CH), 125.29, 117.5, 16.7 (CH_3); MS (EI, 70 eV) *m/z* 77 (32), 83 (85), 107 (57), 124 (37), 268 (82), 285 (100) (M^+), 287 (32) (M+2); HRMS (ESI^+, TOF) calcd for $C_{15}H_{13}ClN_3O$: 286.0747 (M+H). Found: 286.0739.

2-Amino-6-chloro-3-propylquinazolin-4-one (3bh)

Compound **3bh** was prepared by *general procedure 1*. The product (**3bh**, solid, 0.1367 g, 0.576 mmol, 9%, R_f = 0.28 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 171–174 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.80 (d, 1H, *J* = 2.5 Hz), 7.53 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.17–7.16 (m, 3H, *J* = 9.0 Hz, Ar+NH_2), 3.92 (t, 2H, *J* = 7.5 Hz, CH_2), 1.62-1.55 (m, 2H, CH_2), 0.89 (t, 3H, *J* = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.8, 152.2, 148.6, 134.0 (CH), 125.9 (CH), 125.2 (CH), 124.9, 117.0, 42.6 (CH_2), 20.3 (CH_2), 10.9 (CH_3); MS (ESI^+) *m/z* 238 (100) (M+H), 240 (33) (M+H+2); HRMS (ESI^+, TOF) calcd for $C_{11}H_{13}ClN_3O$: 238.0747 (M+H). Found: 238.0721.

2-Amino-6,7-dimethoxy-3-phenylqinazolin-4-one (3ca)

Compound **3ca** was prepared by *general procedure 1*. The product (**3ca**, solid, 1.3160 g, 4.426 mmol, 81%, R_f = 0.23 ($CHCl_3$ / MeOH = 98 : 2)) was purified by

flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 253–256 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.57 (t, 2H, J = 7.0 Hz), 7.51 (t, 1H, J = 7.5 Hz), 7.32 (d, 2H, J = 7.5 Hz), 7.23 (s, 1H), 6.71 (s, 1H), 5.98 (br, 2H, NH_2), 3.85 (s, 3H, Me), 3.77 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 155.6, 151.3, 146.8, 145.7, 136.2, 130.4 (CH), 129.5 (CH), 129.3 (CH), 109.5, 106.7 (CH), 105.7 (CH), 56.14 (CH_3), 56.09 (CH_3); MS (EI, 70 eV) *m/z* 280 (28), 282 (57), 297 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{16}H_{16}N_3O_3$: 298.1192 (M+H). Found: 298.1198.

2-Amino-6,7-dimethoxy-3-(4-tolyl)quinazolin-4-one (3cb)

Compound **3cb** was prepared by *general procedure 1*. The product (**3cb**, solid, 1.2459 g, 4.002 mmol, 96%, R_f = 0.25 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 268 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.36 (d, 2H, J = 8.0 Hz), 7.22 (s, 1H), 7.18 (d, 2H, J = 8.0 Hz), 6.70 (s, 1H), 5.97 (br, 2H, NH_2), 3.85 (s, 3H, Me), 3.77 (s, 3H, Me), 2.40 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.2, 155.0, 151.0, 146.3, 145.2, 138.4, 133.1, 130.4 (CH), 128.6 (CH), 109.0, 106.1 (CH), 105.1 (CH), 55.7 (CH_3), 55.6 (CH_3), 20.8 (CH_3); MS (EI, 70 eV) *m/z* 295 (23), 297 (59) 311 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{17}H_{18}N_3O_3$: 312.1348 (M+H). Found: 312.1343.

2-Amino-6,7-dimethoxy-3-(4-methoxyphenyl)quinazolin-4-one (3cc)

Compound **3cc** was prepared by *general procedure 1*. The product (**3cc**, solid, 1.1525 g, 3.521 mmol, 85%, R_f = 0.35 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 267–270 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.226 (d, 2H, J = 8.8 Hz), 7.225 (s, 1H), 7.08 (d, 2H, J = 8.9 Hz), 6.70 (s, 1H), 5.99 (br, 2H, NH_2), 3.85 (s, 3H, Me), 3.82 (s, 3H, Me), 3.77 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 159.9, 155.5, 151.7, 146.8, 145.6, 130.4 (CH), 128.6, 115.6 (CH), 109.5, 106.7 (CH), 105.6 (CH), 56.11 (CH_3), 56.06 (CH_3), 55.8 (CH_3); MS (EI, 70 eV) *m/z* 312 (58), 327 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{17}H_{18}N_3O_4$: 328.1297 (M+H). Found: 328.1289; Anal. calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.32; H, 5.32; N, 12.91.

2-Amino-3-(4-chlorophenyl)-6,7-dimethoxyquinazolin-4-one (3cd)

Compound **3cd** was prepared by *general procedure 1*. The product (**3cd**, solid, 0.9640 g, 2.906 mmol, 72%, R_f = 0.28 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 298 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.60 (d, 2H, J = 8.5 Hz), 7.36 (d, 2H, J = 8.5 Hz), 7.22 (s, 1H), 6.70 (s, 1H), 6.15 (br, 2H, NH_2), 3.85 (s, 3H, Me), 3.77 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 155.6, 151.2, 146.9, 145.7, 135.2, 134.1, 131.4 (CH), 130.4 (CH), 109.3, 106.6 (CH), 105.6 (CH), 56.14 (CH_3), 56.08 (CH_3); MS (EI, 70 eV) *m/z* 316 (40), 331 (100) (M^+), 333 (36) (M+2); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}ClN_3O_3$: 332.0802 (M+H). Found: 332.0795.

2-Amino-6,7-dimethoxy-3-(4-nitrophenyl)quinazolin-4-one (3ce)

Compound **3ce** was prepared by *general procedure 1*, except the solvent was replaced by 2-methyl-2-butanol, and the reaction time was extended to 12 h. The product (**3ce**, solid, 0.3966 g, 1.158 mmol, 33%, R_f = 0.15 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 315 ^oC (decomp.); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.39 (d, 2H, J = 8.8 Hz), 7.67 (d, 2H, J = 8.4 Hz), 7.23 (s, 1H), 6.71 (s, 1H), 6.25 (br, 2H, NH_2), 3.86 (s, 3H, Me), 3.77 (s, 3H,

Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.0, 155.3, 150.2, 147.8, 146.5, 145.3, 141.9, 131.0 (CH), 125.1 (CH), 108.7, 106.1 (CH), 105.2 (CH), 55.7 (CH_3), 55.6 (CH_3); MS (EI, 20 eV) *m/z* 327 (40), 342 (100) (M^+); HRMS (EI, sector) calcd for $C_{16}H_{14}N_4O_5$: 342.0964. Found: 342.0958.

2-Amino-6,7-dimethoxy-3-(2-tolyl)quinazolin-4-one (3cf)

Compound **3cf** was prepared by *general procedure 1*. The product (**3cf**, solid, 1.3566 g, 4.358 mmol, 86%, R_f = 0.30 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 240 °C ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.44 (dd, 1H, *J* = 7.5, 2.0 Hz), 7.41 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.37 (dt, 1H, *J* = 7.5, 2.0 Hz), 7.25 (s, 1H), 7.22 (d, 1H, *J* = 7.5 Hz), 6.72 (s, 1H), 6.00 (br, 2H, NH_2), 3.86 (s, 3H, Me), 3.78 (s, 3H, Me), 2.02 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.6, 155.2, 150.6, 146.5, 145.3, 135.8, 134.7, 131.2 (CH), 129.3 (CH), 128.8 (CH), 127.6 (CH), 108.8, 106.2 (CH), 105.2 (CH), 55.7 (CH_3), 55.6 (CH_3), 16.8 (CH_3); MS (EI, 70 eV) *m/z* 295 (28), 296 (40), 311 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{17}H_{18}N_3O_3$: 312.1348 (M+H). Found: 312.1349.

2-Amino-6,7-dimethoxy-3-(3-methoxyphenyl)quinazolin-4-one (3cg)

Compound **3cg** was prepared by *general procedure 1*. The product (**3cg**, solid, 1.8308 g, 5.593 mmol, 81%, R_f = 0.38 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 258–260 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.46 (t, 1H, *J* = 8.2 Hz), 7.23 (s, 1H), 7.07 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.92 (d, 1H, *J* = 1.9 Hz), 6.87 (d, 1H, *J* = 7.7 Hz), 6.70 (s, 1H), 6.00 (br, 2H, NH_2), 3.85 (s, 3H, Me), 3.79 (s, 3H, Me), 3.77 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.0, 160.3, 155.1, 150.8, 146.3, 145.2, 136.8, 130.5 (CH), 120.8 (CH), 114.9 (CH), 114.4 (CH), 109.0, 106.1 (CH), 105.1 (CH), 55.61 (CH_3), 55.57 (CH_3), 55.3 (CH_3); MS (ESI^-) *m/z* 326 (100) (M-H); HRMS (ESI^-, TOF) calcd for $C_{17}H_{16}N_3O_4$: 326.1146 (M-H). Found: 326.1149.

2-Amino-6,7-dimethoxy-3-propylquinazolin-4-one (3ch)

Compound **3ch** was prepared by *general procedure 1*. The product (**3ch**, solid, 0.8296 g, 3.151 mmol, 37%, R_f = 0.20 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 183 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.23 (s, 1H), 6.72 (br, 2H, NH_2), 6.61 (s, 1H), 3.92 (t, 2H, *J* = 8.0 Hz, CH_2), 3.82 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 1.61-1.57 (m, 2H, CH_2), 0.88 (t, 3H, *J* = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.0, 154.8, 151.2, 145.9, 145.1, 108.5, 106.1 (CH), 104.8 (CH), 55.53 (CH_3), 55.51 (CH_3), 42.3 (CH_2), 20.5 (CH_2), 10.9 (CH_3); MS (EI, 70 eV) *m/z* 206 (25), 221 (20), 263 (100) (M^+); HRMS (APCI, TOF) calcd for $C_{13}H_{18}N_3O_3$: 264.1348 (M+H). Found: 264.1347.

2-Amino-6-methoxy-3-phenylquinazolin-4-one (3da)

Compound **3da** was prepared by *general procedure 1*. The product (**3da**, solid, 0.4169 g, 1.55 mmol, 52%, R_f = 0.23 (Hex / EtOAc = 8 : 2)) was purified by flash column chromatography (Hex / EtOAc = 8 : 2). m.p. 220–222 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.59–7.50 (m, 3H), 7.35–7.21 (m, 5H), 6.04 (br, 2H, NH_2), 3.78 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 154.2, 150.2, 144.6, 135.6, 129.9 (CH), 129.1 (CH), 128.8 (CH), 125.6 (CH), 124.3 (CH), 116.9, 106.5 (CH), 55.4 (CH_3); MS (EI, 70 eV) *m/z* 134 (17), 252 (51), 266 (43), 267 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O_2$: 267.1008. Found 267.1008.

2-Amino-6-bromo-3-phenylquinazolin-4-one[8] (3ea)

Compound **3ea** was prepared by *general procedure 1*. The product (**3ea**, solid, 0.5789 g, 1.83 mmol, 61%, R_f = 0.20 (Hex / EtOAc = 7 : 3)) was purified by flash column chromatography (Hex / EtOAc = 7 : 3). m.p. 246–247 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.94 (d, 2H, *J* = 2.4 Hz), 7.73 (dd, 1H, *J* = 8.8, 2.4 Hz), 7.60–7.50 (m, 3H), 7.36 (d, 2H, *J* = 6.8 Hz), 7.20 (d, 2H, *J* = 8.8 Hz), 6.44 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.8, 152.1, 149.3, 137.0 (CH), 135.1, 130.0 (CH), 129.3 (CH), 128.7 (CH), 128.3 (CH), 126.4 (CH), 118.3, 112.8; MS (EI, 70 eV) *m/z* 314 (58), 315 (100) (M^+), 317 (96) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{10}BrN_3O$: 315.0007. Found: 315.0010.

[General procedure 2] Preparation of 2-(*N*-substituted-amino)quinazolin-4-one (4) under the optimized TMSCl condition followed by Dimroth rearrangement (Scheme 4)

To a mixture of *N*-substituted cyanamide[4] (**2**, 1.5 equiv) and methyl anthranilate (**1**, 1.0 equiv) in *tert*-butanol (0.5 M) was added trimethylsilyl chloride (1.2 equiv). The mixture was heated at 60 ^{o}C for 4 hours. After cooling to room temperature, the mixture was added aqueous ethanolic NaOH solution (4 N NaOH aqueous solution / EtOH = 1 : 1 (*v*/*v*), 4 times of volume of *t*-BuOH to bring the final reaction concentration to 0.1 M) and the reaction mixture was heated at reflux temperature for 6 hours. The volatile solvents were removed under reduced pressure, and the resulting solution was partitioned between $CHCl_3$ and water. The aqueous layer was acidified with 2 N aqueous acetic acid solution (0.8 equiv to the 4 N NaOH aqueous solution), and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**). An analytical sample of 2-(*N*-substituted-amino)quinazolin-4-one (**4**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)).

2-(*N*-Phenylamino)quinazolin-4-one[9-12] (4aa)

Compound **4aa** was prepared by *general procedure 2*. The product (**4aa**, solid, 0.6351 g, 2.677 mmol, 74%, R_f = 0.16 (Hex / EtOAc = 7 : 3)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 264–265 ^{o}C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.81 (br, 1H, NH), 8.66 (br, 1H, NH), 7.97 (d, 1H, *J* = 7.0 Hz), 7.74 (d, 2H, *J* = 8.0 Hz), 7.65 (t, 1H, *J* = 7.0 Hz), 7.40 (d, 1H, *J* = 8.5 Hz), 7.35 (t, 1H, *J* = 8.0 Hz), 7.23 (t, 1H, *J* = 7.5 Hz), 7.04 (t, 1H, *J* = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 150.0, 147.4, 139.0, 134.4 (CH), 128.8 (CH), 125.9 (CH), 125.3 (CH), 123.0 (CH), 122.5 (CH), 119.3 (CH), 118.4; MS (ESI$^-$) *m/z* 236 (100) (M-H); HRMS (ESI$^-$, TOF) calcd for $C_{14}H_{11}N_3O$: 236.0829 (M-H). Found: 236.0831.

2-(*N*-(4-Tolyl)amino)quinazolin-4-one[9-11] (4ab)

Compound **4ab** was prepared by *general procedure 2*. The product (**4ab**, solid, 0.500 g, 1.989 mmol, 81%, R_f = 0.28 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 275 ^{o}C ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.8 (br, 1H, NH), 8.54 (br, 1H, NH), 7.96 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.63 (t, 1H, *J* = 7.5 Hz), 7.61 (d, 2H, *J* = 8.5 Hz), 7.37 (d, 1H, *J* = 8.5 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 7.15 (d, 2H, *J* = 8.5 Hz), 2.27 (s, 3H, CH_3); ^{13}C NMR

(DMSO-d_6, 125 MHz) δ 161.6, 150.1, 147.5, 136.4, 134.4 (CH), 131.5, 129.2 (CH), 125.9 (CH), 125.3 (CH), 122.8 (CH), 119.5 (CH), 118.3, 20.4 (CH_3); MS (EI, 70 eV) *m/z* 251 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1134.

2-(*N*-(4-Methoxyphenyl)amino)quinazolin-4-one[9-14] (4ac)

Compound **4ac** was prepared by *general procedure 2*. The product (**4ac**, solid, 0.6851 g, 2.563 mmol, 78%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 275–278 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.76 (br, 1H, NH), 8.46 (br, 1H, NH), 7.94 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.64–7.60 (m, 3H), 7.33 (d, 1H, *J* = 7.5 Hz), 7.19 (t, 1H, *J* = 7.5 Hz), 6.93 (d, 2H, *J* = 9.0 Hz), 3.75 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.2, 155.5, 150.8, 148.3, 134.9 (CH), 132.4, 126.4 (CH), 125.6 (CH), 123.1 (CH), 121.9 (CH), 118.7, 114.5 (CH), 55.7 (CH_3); MS (ESI^-) *m/z* 266 (100) (M-H); HRMS (ESI^+, TOF) calcd for $C_{15}H_{12}N_3O_2$: 268.1086 (M+H). Found: 268.1072.

2-(*N*-(4-Chlorophenyl)amino)quinazolin-4-one[9-12,15] (4ad)

Compound **4ad** was prepared by *general procedure 2*. The product (**4ad**, solid, 0.5178 g, 1.91 mmol, 95%, R_f = 0.08 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 280–281 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.91 (br, 1H, NH), 8.85 (br, 1H, NH), 7.99 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.79 (d, 2H, *J* = 8.5 Hz), 7.67 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.42–7.38 (m, 3H), 7.24 (dt, 1H, *J* = 7.5, 1.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.2, 150.2, 147.8, 138.5, 134.9 (CH), 129.1 (CH), 126.5 (CH), 126.4, 125.8 (CH), 123.7 (CH), 121.3 (CH), 118.9; MS (ESI^-) *m/z* 270 (100) (M-H), 272 (22) (M-H+2); HRMS (ESI^-, TOF) calcd for $C_{14}H_9ClN_3O$: 270.0440 (M-H). Found: 270.0433.

2-(*N*-(4-Nitrophenyl)amino)quinazolin-4-one (4ae)

Compound **4ae** was prepared by *general procedure 2*. The product (**4ae**, solid, 0.2089 g, 0.74 mmol, 74%, R_f = 0.23 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 329–330 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.10 (br, 1H, NH), 9.49 (br, 1H, NH), 8.22 (d, 2H, *J* = 9.5 Hz), 8.01 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.99 (d, 2H, *J* = 8.5 Hz), 7.70 (dt, 1H, *J* = 7.8, 1.5 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.30 (t, 1H, *J* = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.3, 149.6, 147.4, 146.1, 141.7, 135.0 (CH), 126.4 (CH), 126.1 (CH), 125.5 (CH), 124.5 (CH), 119.3, 119.0 (CH); MS (ESI^-) *m/z* 281 (100) (M-H); HRMS (ESI^-, TOF) calcd for $C_{14}H_9N_4O_3$: 281.0680 (M-H). Found: 281.0668.

2-(*N*-(2-Tolyl)amino)quinazoline-4-one[11] (4af)

Compound **4af** was prepared by *general procedure 2*. The product (**4af**, solid, 0.7093 g, 2.82 mmol, 94%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 285–290 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.25 (br, 1H, NH), 8.11 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 1H, *J* = 7.5 Hz), 7.91 (br, 1H, NH), 7.61 (t, 1H, *J* = 7.0 Hz), 7.31 (d, 1H, *J* = 8.5 Hz), 7.23–7.21 (m, 2H), 7.21 (t, 1H, *J* = 8.0 Hz), 7.04 (t, 1H, *J* = 7.5 Hz), 2.27 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.8, 150.2, 148.1, 136.8, 134.4 (CH), 130.4 (CH), 129.2, 126.3 (CH), 125.9 (CH), 125.2 (CH), 123.7 (CH), 122.8 (CH), 122.6 (CH), 118.3, 17.9 (CH_3); MS (ESI^+) *m/z* 252 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1120.

2-(*N*-Propylamino)quinazolin-4-one (4ah)

Compound **4ah** was prepared by *general procedure 2*. The product (**4ah**, solid, 0.2489 g, 1.22 mmol, 61%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 189–190 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 10.79 (br, 1H, NH), 7.87 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.55 (dt, 1H, *J* = 7.8, 2.0 Hz), 7.24 (d, 1H, *J* = 8.0 Hz), 7.09 (t, 1H, *J* = 7.5 Hz), 6.29 (br, 1H, NH), 3.28 (m, 2H, propyl), 1.59-1.52 (m, 2H, propyl), 0.92 (t, 3H, *J* = 7.5 Hz, propyl); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.7, 151.3, 134.5 (CH), 126.4 (CH), 124.8, 122.0 (CH), 117.8, 42.4 (CH_2), 22.6 (CH_2), 11.8 (CH_3); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 160.4, 150.8, 139.6, 136.7 (CH), 127.8 (CH), 125.9 (CH), 118.1 (CH), 116.4, 44.1 (CH_2), 22.3 (CH_2), 11.5 (CH_3); MS (ESI^+) *m/z* 204 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{11}H_{14}N_3O$: 204.1137 (M+H). Found: 204.1138.

2-(*N*-(2-Bromophenyl)amino)quinazolin-4-one (4ai)

Compound **4ai** was prepared by *general procedure 2*. The product (**4ai**, light red solid, 0.9385 g, 2.99 mmol, 95%, R_f = 0.21 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 275–276 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 11.46 (br, 1H, NH), 8.33 (br, 1H), 8.17 (br, 1H, NH), 7.96 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.67–7.62 (m, 2H), 7.41 (t, 1H, *J* = 8.5 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 7.8 Hz), 7.06 (t, 1H, *J* = 8.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.0, 148.6, 137.1, 135.2 (CH), 133.3 (CH), 128.8 (CH), 126.6 (CH), 125.8 (CH), 125.6, 124.9 (CH), 124.0 (CH), 119.1, 115.7; MS (EI, 20 eV) *m/z* 236 (100), 315 (13) (M^+), 317 (12) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{10}BrN_3O$: 315.0007. Found: 315.0003.

2-(*N*-(2-Bromo-4-methylphenyl)amino)quinazolin-4-one (4aj)

Compound **4aj** was prepared by *general procedure 2*. The product (**4aj**, white solid, 0.5613 g, 1.70 mmol, 85%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 260–261 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.52 (br, 1H, NH), 8.17 (br, 1H), 8.06 (br, 1H, NH), 7.96 (d, 1H, *J* = 6.8 Hz), 7.62 (t, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 1.2 Hz), 7.32 (d, 1H, *J* = 8.4 Hz), 7.22 (t, 2H, *J* = 7.4 Hz), 2.29 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.3, 150.3, 148.3, 135.3, 134.8 (CH), 134.3, 133.1 (CH), 129.2 (CH), 126.4 (CH), 125.7 (CH), 124.8 (CH), 123.6 (CH), 118.9, 115.5, 20.4 (CH_3); MS (EI, 20 eV) *m/z* 250 (100), 329 (13) (M^+), 331 (13) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}BrN_3O$: 329.0164. Found: 329.0168.

2-(*N*-(2-Bromo-4-fluorophenyl)amino)quinazolin-4-one (4ak)

Compound **4ak** was prepared by *general procedure 2*. The product (**4ak**, white solid, 0.9824 g, 2.94 mmol, 95%, R_f = 0.10 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 266–267 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.52 (br, 1H, NH), 8.24 (br, 2H, Ar+NH), 7.96 (dd, 1H, *J* = 7.6, 0.8 Hz), 7.66–7.60 (m, 2H), 7.34–7.29 (m, 2H), 7.23 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.4, 158.5 (d, *J* = 243 Hz), 149.8, 148.3, 134.9 (CH), 133.9, 126.44 (CH), 126.37, 125.4, 123.6 (CH), 119.9 (d, *J* = 26.0 Hz, CH), 118.8, 116.6, 115.5 (d, *J* = 22.0 Hz, CH); ^{19}F NMR (DMSO-d_6, 375 MHz) δ -117.0; MS (EI, 20 eV) *m/z* 254 (100), 333 (12) (M^+), 335 (13) (M+2); HRMS (EI, sector) calcd for $C_{14}H_9BrFN_3O$: 332.9913. Found: 332.9908.

6-Chloro-2-(*N*-phenylamino)quinazolin-4-one[10] (4ba)

Compound **4ba** was prepared by *general procedure 2*. The product (**4ba**, solid, 0.7742 g, 2.85 mmol, 95%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 294–295 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.98 (br, 1H, NH), 8.73 (br, 1H, NH), 7.87 (d, 1H, *J* = 2.5 Hz), 7.71 (d, 2H, *J* = 8.0 Hz), 7.63 (dd, 1H, *J* = 8.7, 2.6 Hz), 7.40 (d, 1H, *J* = 8.8 Hz), 7.35 (t, 2H, *J* = 7.8 Hz), 7.05 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.3, 149.4, 148.3, 139.2, 134.9 (CH), 129.4 (CH), 128.0, 127.5 (CH), 125.3 (CH), 123.3 (CH), 120.1 (CH), 120.0; MS (ESI^-) *m/z* 270 (100) (M-H), 272 (25) (M-H+2); HRMS (ESI^-, TOF) calcd for $C_{14}H_9ClN_3O$: 270.0440 (M-H). Found: 270.0450.

6-Chloro-2-(*N*-(4-tolyl)amino)quinazolin-4-one (4bb)

Compound **4bb** was prepared by *general procedure 2*. The product (**4bb**, solid, 0.4920 g, 1.721 mmol, 52%, R_f = 0.30 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 300 ^oC (decomp.); ^1H NMR (DMSO-d_6, 500 MHz) δ 10.94 (br, 1H, NH), 8.60 (br, 1H, NH), 7.86 (d, 1H, *J* = 2.5 Hz), 7.63 (dd, 1H, *J* = 9.0, 2.5 Hz),7.58 (d, 2H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* = 9.0 Hz), 7.14 (d, 2H, *J* = 8.0 Hz), 2.27 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.7, 149.0, 147.9, 136.1, 134.3 (CH), 131.8, 129.2 (CH), 127.4 (CH), 126.7, 124.8 (CH), 119.7 (CH), 119.4, 20.4 (CH_3); MS (EI, 70 eV) *m/z* 124 (26), 285 (100) (M^+), 287 (32) (M+2); HRMS (ESI^+, TOF) calcd for $C_{15}H_{13}ClN_3O$: 286.0747 (M+H). Found: 286.0748.

6-Chloro-2-(*N*-(4-methoxyphenyl)amino)quinazolin-4-one (4bc)

Compound **4bc** was prepared by *general procedure 2*. The product (**4bc**, solid, 0.1590 g, 0.556 mmol, 81%, R_f = 0.25 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 325 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 10.97 (br, 1H, NH), 8.56 (br, 1H, NH), 7.86 (d, 1H, *J* = 2.5 Hz), 7.62 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.59 (d, 2H, *J* = 8.5 Hz), 7.35 (d, 1H, *J* = 9.0 Hz), 6.93 (d, 2H, *J* = 9.0 Hz), 3.75 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125MHz) δ 160.8, 155.2, 149.1, 148.2, 134.3 (CH), 131.5, 127.2 (CH), 126.5, 124.8 (CH), 121.7 (CH), 119.2, 114.0 (CH), 55.2 (CH_3); MS (EI, 70 eV) *m/z* 301 (100) (M^+), 303 (25) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}ClN_3O_2$: 301.0618. Found: 301.0616.

6-Chloro-2-(*N*-(4-nitrophenyl)amino)quinazolin-4-one (4be)

Compound **4be** was prepared by *general procedure 2*. The product (**4be**, solid, 0.1520 g, 0.48 mmol, 48%, R_f = 0.05 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 354–355 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 11.50 (br, 1H, NH), 10.11 (br, 1H, NH), 8.21 (d, 2H, *J* = 9.0 Hz), 7.99 (d, 2H, *J* = 9.0 Hz), 7.90 (d, 1H, *J* = 2.5 Hz), 7.69 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.48 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.2, 148.4, 147.9, 145.9, 141.8, 134.9 (CH), 128.4, 128.2 (CH), 125.5 (CH), 125.3 (CH), 120.5, 118.9 (CH); MS (ESI^-) *m/z* 315 (100) (M-H), 317 (20) (M-H+2); HRMS (ESI^-, TOF) calcd for $C_{14}H_8ClN_4O_3$: 315.0290 (M-H). Found: 315.0283.

6-Chloro-2-(*N*-(2-tolyl)amino)quinazolin-4-one (4bf)

Compound **4bf** was prepared by *general procedure 2*. The product (**4bf**, solid, 0.2328 g, 0.814 mmol, 81%, R_f = 0.48 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 289–290 ^oC; ^1H NMR

(DMSO-d_6, 500 MHz) δ 11.41 (br, 1H, NH), 8.04 (s, 1H), 8.00 (br, 1H, NH), 7.87 (d, 1H, *J* = 2.5 Hz), 7.60 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.31 (d, 1H, *J* = 9.0 Hz), 7.23 (d, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 8.0 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 2.26 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.9, 149.1, 148.6, 136.5, 134.3 (CH), 130.3 (CH), 129.5, 127.3 (CH), 126.7, 126.3 (CH), 124.8 (CH), 124.0 (CH), 122.9 (CH), 119.3, 17.8 (CH_3); MS (EI, 70 eV) *m/z* 124 (28), 131 (56), 154 (30), 269 (66), 285 (100) (M^+), 287 (31) (M+2); HRMS (ESI^+, TOF) calcd for $C_{15}H_{13}ClN_3O$: 286.0747 (M+H). Found: 286.0742.

6-Chloro-2-(*N*-propylamino)quinazolin-4-one (4bh)

Compound **4bh** was prepared by *general procedure 2*. The product (**4bh**, solid, 0.7456 g, 3.14 mmol, 52%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 272–273 ^oC; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.95 (br, 1H, NH), 7.78 (d, 1H, *J* = 2.5 Hz), 7.54 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.25 (d, 1H, *J* = 9.0 Hz), 6.39 (br, 1H, NH), 3.29-3.25 (m, 2H, propyl), 1.58-1.51 (m, 2H, propyl), 0.90 (t, 3H, *J* = 7.5 Hz, propyl); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.7, 151.5, 150.4, 134.5 (CH), 127.1 (CH), 125.9, 125.3 (CH), 118.9, 42.4 (CH_2), 22.6 (CH_2), 11.8 (CH_3); MS (ESI^-) *m/z* 236 (100) (M-H), 238 (23) (M-H+2); HRMS (ESI^-, TOF) calcd for $C_{11}H_{11}ClN_3O$: 236.0596 (M-H). Found: 236.0590.

6,7-Dimethoxy-2-(*N*-phenylamino)quinazolin-4-one[16] (4ca)

Compound **4ca** was prepared by *general procedure 2*. The product (**4ca**, solid, 0.6957 g, 2.34 mmol, 78%, R_f = 0.10 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 256–257 ^oC; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.64 (br, 1H, NH), 8.54 (br, 1H, NH), 7.73 (d, 2H, *J* = 7.5 Hz), 7.35 (dd, 2H, *J* = 7.5, 1.0 Hz), 7.32 (s, 1H), 7.02 (t, 1H, *J* = 7.5 Hz), 6.90 (s, 1H), 3.88 (s, 3H, Me), 3.81 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.4, 155.4, 147.2, 146.6, 146.5, 139.7, 129.3 (CH), 122.6 (CH), 119.5 (CH), 111.1, 107.2 (CH), 106.0 (CH), 56.3 (CH_3), 56.1 (CH_3); MS (ESI^-) *m/z* 296 (100) (M-H); HRMS (ESI^-, TOF) calcd for $C_{16}H_{14}N_3O_3$: 296.1041 (M-H). Found: 296.1055.

6,7-Dimethoxy-2-(*N*-(4-tolyl)amino)quinazolin-4-one (4cb)

Compound **4cb** was prepared by *general procedure 2*. The product (**4cb**, solid, 0.3917 g, 1.258 mmol, 80%, R_f = 0.10 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 276 ^oC ($CHCl_3$ / MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.03 (br, 1H, NH), 7.56 (d, 2H, *J* = 8.5 Hz), 7.32 (s, 1H), 7.18 (d, 2H, *J* = 8.5 Hz), 6.92 (s, 1H), 3.87 (s, 3H, Me), 3.81 (s, 3H, Me), 2.29 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.7, 154.9, 147.4, 146.2, 135.6, 132.2, 129.4 (CH), 129.2, 120.3 (CH), 110.1, 105.7 (CH), 105.4 (CH), 55.8 (CH_3), 55.6 (CH_3), 20.4 (CH_3); MS (EI, 70 eV) *m/z* 295 (25), 311 (100) (M^+); HRMS (ESI^+, TOF) calcd for $C_{17}H_{18}N_3O_3$: 312.1348 (M+H). Found: 312.1354.

6,7-Dimethoxy-2-(*N*-(4-methoxyphenyl)amino)quinazolin-4-one[14] (4cc)

Compound **4cc** was prepared by *general procedure 2*. The product (**4cc**, solid, 0.4976 g, 1.52 mmol, 76%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 251–252 ^oC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.61 (br, 1H, NH), 8.34 (br, 1H, NH), 7.60 (d, 2H, *J* = 9.2 Hz), 7.30 (s, 1H), 6.92 (d, 2H, *J* = 9.2 Hz), 6.83 (s, 1H), 3.86 (s, 3H, Me), 3.80 (s, 3H, Me), 3.74 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.5, 155.32, 155.30, 147.6, 146.8, 146.4, 132.7, 121.7 (CH), 114.5 (CH), 110.8, 107.0 (CH), 106.0 (CH),

56.2 (CH_3), 56.1 (CH_3), 55.7 (CH_3); MS (ESI^-) *m/z* 326 (100) (M-H); HRMS (ESI^-, TOF) calcd for $C_{17}H_{16}N_3O_4$: 326.1146 (M-H). Found: 326.1160.

2-(*N*-(4-Chlorophenyl)amino)-6,7-dimethoxyquinazolin-4-one (4cd)

Compound **4cd** was prepared by *general procedure 2*. The product (**4cd**, solid, 2.0960 g, 6.32 mmol, 90%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 287–288 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.71 (br, 1H, NH), 8.70 (br, 1H, NH), 7.76 (d, 2H, *J* = 8.7 Hz), 7.37 (d, 2H, *J* = 8.8 Hz), 7.32 (s, 1H), 6.90 (s, 1H), 3.88 (s, 3H, Me), 3.81 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.9, 154.9, 146.5, 146.3, 145.8, 138.2, 128.6 (CH), 125.6, 120.5 (CH), 110.7, 106.7 (CH), 105.5 (CH), 55.8 (CH_3), 55.6 (CH_3); MS (EI, 70 eV) *m/z* 164 (26), 315 (21), 331 (100) (M^+), 333 (37) (M+2); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}ClN_3O_3$: 332.0802 (M+H). Found: 332.0801.

6,7-Dimethoxy-2-(*N*-(4-nitrophenyl)amino)quinazolin-4-one (4ce)

Compound **4ce** was prepared by *general procedure 2*. The product (**4ce**, solid, 0.3402 g, 0.99 mmol, 95%, R_f = 0.06 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 321–322 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 11.53 (br, 1H, NH), 8.21 (d, 2H, *J* = 9.0 Hz), 8.17 (d, 2H, *J* = 9.5 Hz), 7.41 (s, 1H), 7.00 (s, 1H), 3.91 (s, 3H, Me), 3.85 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.9, 155.2, 148.9, 147.5, 147.0, 146.2, 140.8, 125.5 (CH), 118.2 (CH), 111.8, 107.1 (CH), 106.1 (CH), 56.3 (CH_3), 56.1 (CH_3); MS (ESI^+) *m/z* 343 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}N_4O_5$: 343.1042 (M+H). Found: 343.1043.

6,7-Dimethoxy-2-(*N*-(2-tolyl)amino)quinazoline-4-one (4cf)

Compound **4cf** was prepared by *general procedure 2*. The product (**4cf**, light yallow solid, 0.9111 g, 2.93 mmol, 95%, R_f = 0.13 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 262–263 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 11.13 (br, 1H, NH), 8.15 (d, 1H, *J* = 8.4 Hz), 7.77 (br, 1H, NH), 7.32 (s, 1H), 7.22 (t, 1H, *J* = 7.0 Hz), 7.21 (d, 1H, *J* = 8.0 Hz), 7.01 (t, 1H, *J* = 7.4 Hz), 6.80 (s, 1H), 3.85 (s, 3H, Me), 3.80 (s, 3H, Me), 2.26 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 155.3, 147.8, 146.8, 146.5, 137.5, 130.7 (CH), 129.2, 126.7 (CH), 123.8 (CH), 122.7 (CH), 111.0, 107.0 (CH), 106.0 (CH), 56.2 (CH_3), 56.1 (CH_3), 18.4 (CH_3); MS (EI, 70 eV) *m/z* 180, (45), 296 (54), 311 (100) (M^+); HRMS (EI, sector) calcd for $C_{17}H_{17}N_3O_3$: 311.1270 (M^+). Found: 311.1269.

6,7-Dimethoxy-2-(*N*-(3-methoxyphenyl)amino)quinazolin-4-one (4cg)

Compound **4cg** was prepared by *general procedure 2*. The product (**4cg**, solid, 0.4380 g, 1.338 mmol, 84%, R_f = 0.30 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 227–230 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.63 (br, 1H, NH), 8.56 (br, 1H, NH), 7.48 (s, 1H), 7.32 (s, 1H), 7.23 (t, 1H, *J* = 8.0 Hz), 7.19 (d, 1H, *J* = 8.0 Hz), 6.88 (s, 1H), 6.60 (d, 1H, *J* = 7.8 Hz), 3.88 (s, 3H, Me), 3.81 (s, 3H, Me), 3.77 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.9, 159.7, 154.9, 146.6, 146.2, 146.0, 140.4, 129.6 (CH), 111.4 (CH), 110.6, 107.3 (CH), 106.7 (CH), 105.5 (CH), 105.1 (CH), 55.8 (CH_3), 55.6 (CH_3), 55.0 (CH_3); MS (ESI^-) *m/z* 326 (100) (M-H); HRMS (ESI^-, TOF) calcd for $C_{17}H_{16}N_3O_4$: 326.1146 (M-H). Found: 326.1160.

6,7-Dimethoxy-2-(*N*-propylamino)quinazolin-4-one[17] (4ch)

Compound **4ch** was prepared by *general procedure 2*. The product (**4ch**, light yellow solid, 1.2322 g, 4.68 mmol, 78%, R_f = 0.11 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. 282–284 ^oC; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.28 (s, 1H), 6.95 (br, 1H), 3.86 (s, 3H, Me), 3.80 (s, 3H, Me), 3.33-3.32 (m, 2H, propyl), 1.60-1.56 (m, 2H, propyl), 0.93 (t, 3H, *J* = 7.5 Hz); ^1H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.84 (br, 1H, NH), 7.33 (s, 1H), 7.12 (br, 1H), 3.87 (s, 3H, Me), 3.81 (s, 3H, Me), 3.38–3.32 (m, 2H, propyl), 1.60–1.56 (m, 2H, propyl), 0.93 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.8, 155.5, 150.4, 146.4, 109.1, 106.6 (CH), 103.6 (CH), 56.4 (CH_3), 56.2 (CH_3), 42.9 (CH_2), 22.4 (CH_2), 11.7 (CH_3); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 156.6, 150.5, 148.1, 135.4, 108.7, 107.7 (CH), 100.5 (CH), 57.0 (CH_3), 56.7 (CH_3), 44.2 (CH_2), 22.5 (CH_2), 11.7 (CH_3); MS (ESI^+) *m/z* 264 (100) (M+1); HRMS (ESI^+, TOF) calcd for $C_{13}H_{18}N_3O_3$: 264.1348 (M+H). Found: 264.1350

6-Methoxy-2-(*N*-phenylamino)quinazolin-4-one (4da)

Compound **4da** was prepared by *general procedure 2*. The product (**4da**, soild, 0.1016 g, 0.380 mmol, 13%, R_f = 0.27 (Hex / EtOAc = 8 : 2) was purified by flash column chromatography (Hex / EtOAc = 7 : 3). m.p. 259–260 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.81 (br, 1H, NH), 8.54 (br, 1H, NH), 7.72 (d, 2H, *J* = 7.6 Hz), 7.39–7.28 (m, 5H), 7.02 (t, 1H, *J* = 7.2 Hz), 3.82 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.4, 155.3, 146.0, 144.3, 139.2, 128.8 (CH), 126.9 (CH), 123.9 (CH), 122.2 (CH), 118.9 (CH), 118.7, 106.2 (CH), 55.4 (CH_3); MS (EI, 70 eV) *m/z* 252 (29), 266 (47), 267 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O_2$: 267.1008. Found 267.1008.

6-Bromo-2-(*N*-phenylamino)quinazolin-4-one[18] (4ea)

Compound **4ea** was prepared by *general procedure 2*. The product (**4ea**, soild, 0.2787 g, 0.88 mmol, 29%, R_f = 0.14 (Hex / EtOAc = 7 : 3) was purified by flash column chromatography (Hex / EtOAc = 7 : 3). m.p. 289–290 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.98 (br, 1H, NH), 8.73 (br, 1H, NH), 8.02 (d, 1H, *J* = 2.4 Hz), 7.76 (dd, 1H, *J* = 8.7, 2.4 Hz), 7.72 (d, 2H, *J* = 8.0 Hz), 7.37–7.33 (m, 3H), 7.06 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.5, 149.1, 147.8, 138.7 (CH), 137.1, 128.8 (CH), 127.9 (CH), 127.7 (CH), 122.7 (CH), 120.0, 119.5 (CH), 114.7; MS (EI, 70 eV) *m/z* 314 (75), 315 (100) (M^+), 317 (99) (M+2); HRMS (EI, sector) calcd for $C_{14}H_{10}BrN_3O$: 315.0007. Found: 315.0009.

[General procedure 3] Preparation of 3-substituted 2-aminoquinazolin-4-one (3) and 2-(*N*-substituted-amino)quinazolin-4-one (4) from corresponding anthranilic acids (5) under the optimized *p*-TsOH condition (Scheme 6)

To a mixture of *N*-substituted cyanamide[4] (**2**, 1.5 equiv) and anthranilic acid (**5**, 1.0 equiv) in *tert*-butanol (0.5 M) was added *p*-toluenesulfonic acid monohydrate (1.2 equiv). The mixture was heated at reflux temperature for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ and 2 N NaOH aqueous solution. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 3-substituted 2-aminoquinazolin-4-one (**3**). An analytical sample of 3-substituted 2-aminoquinazolin-4-one (**3**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)). The regioisomer, 2-(*N*-substituted-amino)quinazolin-4-one (**4**), was retrieved by acidifying

the aqueous layer with 2 N aqueous acetic acid solution (0.8 equiv to the 2 N NaOH aqueous solution) followed by $CHCl_3$ extraction. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**).

2-Amino-6-chloro-3-(4-chlorophenyl)quinazolin-4-one (3bd)

Compound **3bd** was prepared by *general procedure 3*. The product (**3bd**, solid, 0.6227 g, 2.034 mmol, 47%, R_f = 0.30 ($CHCl_3$ / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 315–317 ^oC ($CHCl_3$ / MeOH); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.79 (d, 1H, *J* = 2.5 Hz), 7.62 (d, 2H, *J* = 8.5 Hz), 7.61 (dd, 1H, *J* = 8.5, 3.0 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 6.59 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.4, 152.4, 149.5, 134.9 (CH), 134.6, 134.4, 131.3 (CH), 130.5 (CH), 126.6 (CH), 125.7 (CH), 125.6, 118.1; MS (EI, 70 eV) *m/z* 305 (100) (M^+), 307 (62) (M+2), 309 (17) (M+4); HRMS (ESI^+, TOF) calcd for $C_{14}H_{10}C_{l2}N_3O$: 306.0201 (M+H). Found: 306.0193.

2-Amino-6-methoxy-3-(4-tolyl)quinazolin-4-one (3db)

Compound **3db** was prepared by *general procedure 3*. The product (**3db**, solid, 0.2457 g, 0.873 mmol, 44%, R_f = 0.3 (CH_2Cl_2 / MeOH = 99 : 1) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 259-260 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.37 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 2.8 Hz), 7.26 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.21 (d+d, 2H+1H, *J* = 8.4 Hz), 6.06 (br, 2H, NH_2), 3.78 (s, 3H, Me), 2.40 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 154.2, 150.4, 144.5, 138.5, 133.0, 130.4 (CH), 128.5 (CH), 125.6 (CH), 124.2 (CH), 116.9, 106.4 (CH), 55.4 (CH_3), 20.8 (CH_3); MS (ESI^+) *m/z* 282 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}N_3O_2$: 282.1243 (M+H). Found: 282.1245.

2-Amino-6-methyl-3-phenylquinazolin-4-one[19] (3fa)

Compound **3fa** was prepared by *general procedure 3*. The product (**3fa**, soild, 0.3944 g, 1.57 mmol 59%, R_f = 0.13 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2). m.p. 212–218 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.69 (s, 1H), 7.57 (t, 2H, *J* = 7.0 Hz), 7.51 (t, 1H, *J* = 7.3 Hz), 7.44 (dd, 1H, *J* = 8.4, 2.1 Hz), 7.34 (d, 2H, *J* = 7.2 Hz), 7.17 (d, 1H, *J* = 8.3 Hz), 6.13 (br, 2H, NH_2), 2.34 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 151.1, 148.0, 135.8 (CH), 135.6, 130.6, 129.9 (CH), 129.1 (CH), 128.8 (CH), 125.7 (CH), 123.9 (CH), 116.5, 20.5 (CH_3); MS (EI, 70 eV) m/z 250 (95), 251 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O$: 251.1059. Found: 251.1059.

2-Amino-6-methyl-3-(4-tolyl)quinazolinone (3fb)

Compound **3fb** was prepared by *general procedure 3*. The product (**3fb**, solid, 0.193 g, 0.413 mmol, 41%, R_f = 0.5 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 258–260 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.68 (s, 1H), 7.43 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 6.11 (br, 2H, NH_2), 2.40 (s, 3H, Me), 2.34 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 151.2, 148.0, 138.4, 135.7 (CH), 132.9, 130.5, 130.4 (CH), 128.5 (CH), 125.7 (CH), 123.8 (CH), 116.5, 20.8 (CH_3), 20.4 (CH_3); MS (ESI^+) *m/z* 266.38 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}N_3O$: 266.1293 (M+H). Found: 265.1296.

2-Amino-3-(4-chlorophenyl)-6-methylquinazolin-4-one (3fd)

Compound **3fd** was prepared by *general procedure 3*. The product (**3fd**, soild, 0.1100 g, 0.296 mmol, 37%, R_f = 0.25 (CH_2Cl_2 / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2). m.p. 298 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.68 (s, 1H), 7.61 (d, 2H, *J* = 8.7 Hz), 7.44 (dd, 1H, *J* = 8.4, 2.2 Hz), 7.39 (d, 2H, *J* = 8.5 Hz), 7.15 (d, 1H, *J* = 8.3 Hz), 6.27 (br, 2H, NH_2), 2.34 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 150.9, 148.1, 135.8 (CH), 134.5, 133.7, 130.9 (CH), 130.6, 130.0 (CH), 125.7 (CH), 123.9 (CH), 116.3, 20.5 (CH_3); MS (EI, 70 eV) *m/z* 84 (22), 159 (22), 284 (100), 285 (88) (M^+), 287 (25) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}ClN_3O$: 285.0669. Found: 285.0662.

2-Amino-6-hydroxy-3-(4-tolyl)quinazolin-4-one (3gb)

Compound **3gb** was prepared by *general procedure 3*. The product (**3gb**, soild, 0.1523 g, 0.296 mmol, 57%, R_f = 0.11 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2); m.p. 287 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.51 (br, 1H, OH), 7.36 (d, 2H, *J* = 8.1 Hz), 7.23 (d, 1H, *J* = 2.1 Hz), 7.18 (d, 2H, *J* = 8.2 Hz), 7.14–7.08 (m, 2H, Ar), 5.85 (br, 2H, NH_2), 2.39 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 152.4, 149.9, 143.1, 138.7, 133.1, 130.6 (CH), 128.6 (CH), 125.5 (CH), 124.4 (CH), 117.4, 109.5 (CH), 21.0 (CH_3); MS (EI, 70 eV) *m/z* 266 (90), 267 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O_2$: 267.1008. Found: 267.1010.

[General procedure 4] Preparation of 2-(*N*-substituted-amino)quinazolin-4-one (4) from corresponding anthranilic acids (5) under the optimized TMSCl condition followed by Dimroth rearrangement (Scheme 7)

To a mixture of *N*-substituted cyanamide[4] (**2**, 1.5 equiv) and anthranilic acid (**1**, 1.0 equiv) in *tert*-butanol (0.5 M) was added trimethylsilyl chloride (1.2 equiv). The mixture was heated at 60 ^oC for 4 hours. After cooling to room temperature, the mixture was added aqueous ethanolic NaOH solution (4 N NaOH aqueous solution / EtOH = 1 : 1 (*v*/*v*), 4 times of volume of *t*-BuOH to bring the final reaction concentration to 0.1 M) and the reaction mixture was heated at reflux temperature for 6 hours. The volatile solvents were removed under reduced pressure, and the resulting solution was partitioned between $CHCl_3$ and water. The aqueous layer was acidified with 2 N aqueous acetic acid solution (0.8 equiv to the 4 N NaOH aqueous solution), and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give 2-(*N*-substituted-amino)quinazolin-4-one (**4**). An analytical sample of 2-(*N*-substituted-amino)quinazolin-4-one (**4**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 5 (*v*/*v*)).

6-Chloro-2-(*N*-(4-chlorophenyl)amino)quinazolinone (4bd)

Compound **4bd** was prepared by *general procedure 4*. The product (**4bd**, solid, 0.8437 g, 2.755 mmol, 68%, R_f = 0.25 ($CHCl_3$ / MeOH = 98 : 2) was purified by flash column chromatography ($CHCl_3$ / MeOH = 99 : 1). m.p. >320 ^oC (IPA / DMF); ^1H NMR (DMSO-d_6, 500 MHz) δ 11.04 (br, 1H, NH), 8.85 (br, 1H, NH), 7.89 (d, 1H, *J* = 2.5 Hz), 7.75 (d, 2H, *J* = 8.5 Hz), 7.67 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.42 (d, 1H, *J* = 8.5 Hz), 7.39 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.1, 149.1, 148.1, 138.2, 134.9 (CH), 129.1 (CH), 128.0 (CH), 127.6, 126.8, 125.3 (CH), 121.6 (CH),

120.1; MS (ESI^+) *m/z* 306 (100) (M+H), 308 (55) (M+H+2), 310 (9) (M+H+4); HRMS (ESI^+, TOF) calcd for $C_{14}H_{10}Cl_2N_3O$: 306.0201 (M+H). Found: 306.0200.

6-Methoxy-2-(*N*-(4-tolyl)amino)quinazolinone (4db)

Compound **4db** was prepared by *general procedure 4*. The product (**4db**, solid, 0.2134 g, 0.759 mmol, 76%, R_f = 0.1 (CH_2Cl_2 / MeOH = 99 : 1) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2). m.p. 277–278 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.81 (br, 1H, NH), 8.46 (br, 1H, NH), 7.59 (d, 2H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* = 2.8 Hz), 7.35 (d, 1H, *J* = 8.8 Hz), 7.27 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.14 (d, 2H, *J* = 8.4 Hz), 3.81 (s, 3H, Me), 2.27 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.5, 155.2, 146.2, 144.4, 136.6, 131.1 129.2 (CH), 126.8 (CH), 123.8 (CH), 119.1 (CH), 118.5, 106.2 (CH), 55.4 (CH_3), 20.4 (CH_3); MS (ESI^+) *m/z* 282 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}N_3O_2$: 282.1243 (M+H). Found: 282.1242.

6-Methyl-2-(*N*-phenylamino)quinazolin-4-one (4fa)

Compound **4fa** was prepared by *general procedure 4*. The product (**4fa**, soild, 0.1704 g, 0.67 mmol, 51%, R_f = 0.08 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2). m.p. 268–275 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.74 (br, 1H, NH), 8.61 (br, 1H, NH), 7.77 (s, 1H), 7.73 (d, 2H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.6 Hz), 7.34 (t, 2H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 8.2 Hz), 7.03 (t, 1H, *J* = 7.7 Hz), 2.37 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.5, 147.9, 146.8, 139.1, 135.7 (CH), 132.3, 128.8 (CH), 125.24 (CH), 125.22 (CH), 122.3 (CH), 119.1 (CH), 118.1, 20.5 (CH_3); MS (ESI^+) *m/z* 252 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{15}H_{14}N_3O$: 252.1137 (M+H). Found: 252.1139.

6-Methyl-2-(*N*-(4-tolyl)amino)quinazolinone[20] (4fb)

Compound **4fb** was prepared by *general procedure 4*. The product (**4fb**, solid, 0.1624 g, 0.612 mmol, 61%, R_f = 0.2 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 99 : 1). m.p. 277–280 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.76 (br, 1H, NH), 8.54 (br, 1H, NH), 7.75 (s, 1H), 7.60 (d, 2H, *J* = 8.0 Hz), 7.46 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.29 (d, 1H, *J* = 8.4 Hz), 7.15 (d, 2H, *J* = 8.4 Hz), 2.36 (s, 3H, Me), 2.27 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 148.0, 147.0, 136.5, 135.7 (CH), 132.1, 131.3, 129.2 (CH), 125.3 (CH), 125.2 (CH), 119.3 (CH), 118.0, 20.5 (CH_3), 20.4 (CH_3); MS (ESI^+) *m/z* 266 (100) (M+H); HRMS (ESI^+, TOF) calcd for $C_{16}H_{15}N_3O$: 266.1293 (M+H). Found: 266.1295.

2-(*N*-(4-Chlorophenyl)amino)-6-methylquinazolin-4-one (4fd)

Compound **4fd** was prepared by *general procedure 4*. The product (**4fd**, soild, 0.1336 g, 0.46 mmol, 58%, R_f = 0.20 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2). m.p. 275 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.84 (br, 1H, NH), 8.81 (br, 1H, NH), 7.78 (d, 2H, *J* = 6.8 Hz), 7.77 (s, 1H), 7.49 (d, 1H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 8.8 Hz), 7.33 (d, 1H, *J* = 8.2 Hz), 2.37 (s, 3H, Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.0, 147.6, 144.9, 137.1, 135.9 (CH), 133.1, 128.9 (CH), 127.1, 125.6 (CH), 123.3 (CH), 122.0 (CH), 117.7, 20.4 (CH_3); MS (EI, 70 eV) *m/z* 284 (88), 285 (100) (M^+), 287 (36) (M+2); HRMS (EI, sector) calcd for $C_{15}H_{12}ClN_3O$: 285.0669. Found: 285.0670.

6-Hydroxy-2-(*N*-(4-tolyl)amino)quinazolin-4-one (4gb)

Compound **4gb** was prepared by *general procedure 4*. The product (**4gb**, soild, 0.3255 g, 1.21 mmol, 70%, R_f = 0.05 (CH_2Cl_2 / MeOH = 98 : 2) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 96 : 4); m.p. 180 ^oC; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.02 (br, 1H, NH), 9.48 (br, 1H, OH), 7.83 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 2.6 Hz), 7.21 (d, 1H, *J* = 8.7 Hz), 7.08 (d, 2H, *J* = 8.7 Hz), 7.06 (dd, 1H, *J* = 8.2, 2.9 Hz), 2.26 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.7, 153.4, 145.6, 143.1, 136.9, 131.0 (CH), 129.3 (CH), 126.7 (CH), 123.9 (CH), 119.0, 118.9, 109.2 (CH), 20.4 (CH_3); MS (EI, 70 eV) *m/z* 266 (95), 267 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{13}N_3O_2$: 267.1008. Found: 267.1007.

[General procedure 5] Preparation of benzimidazo[2,1-*b*]quinazolin-12-one derivatives (9) from 3-(2-bromophenyl)-2-aminoquinazolin-4-ones (3ai-3ak) or 2-(*N*-(2-bromophenyl)amino)quinazolin-4-ones (4ai-4ak) (Scheme 9)

To a mixture of *N*-(2-bromophenyl)-substituted 2-aminoquinazolin-4-one (**3ai-ak** or **4ai-ak**) (1.0 equiv), L-proline (0.2 equiv), and potassium carbonate (4.0 equiv) in DMF (0.2 M) was added copper(I) iodide (0.1 equiv) at room temperature. The flask was capped with septum, and then evacuated and backfilled with argon gas for three times. The reaction mixture was stirred at 120 ^oC for 8 hours (for **3ai-ak**) or 24 hours (for **4ai-ak**). The solvent was removed by reduced pressure, and the residue was partitioned between $CHCl_3$ and saturated aqueous NH_4OAc solution. The organic layer was concentrated under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ and *conc.* aqueous NH_4OH solution (1 : 1 (*v*/*v*), 0.1 M) and the mixture was stirred at room temperature for 1.5 hours (The purpose was to separate the trace amount of copper residue from the product.). The resulting undissolved solid was collected. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was combined with the undissolved solid and purified with flash column chromatography to give benzimidazo[2,1-*b*]quinazolin-12-one (**9**). An analytical sample of benzimidazo[2,1-*b*]quinazolin-12-one (**9**) was obtained by recrystallization from $CHCl_3$ / MeOH or $CHCl_3$ / EtOH (approximately 1 : 1 (*v*/*v*)).

During structural characterization of benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) with NMR spectroscopy, we observed obscure ^{13}C NMR spectra with indistinct and broad peaks as well as obvious missing peaks, particularly for the quaternary carbons. We rationalized that the nitrogen-bonded protons of benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) can rapidly hopping among the basic nitrogens inter- and intra-molecularly in solution. The dynamic process involves at least the equilibrium between two non-equivalent structures and the transient states in between, which caused significant peak broadening due to non-equivalent environments for the carbons nearby the basic nitrogens. Therefore, for NMR spectroscopic characterization purpose, an additional set of ^1H & ^{13}C NMR spectra for benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) were acquired with the addition of one drop of TFA, which was intended to saturate the basic nitrogen sites with additional proton source to prevent the proton transfer. As a result, the carbon skeletons of benzimidazo[2,1-*b*]quinazolin-12-ones (**9**) were confirmed unambiguously by both unprotonated and protonated ^{13}C NMR spectra.

Benzimidazo[2,1-*b*]quinazolin-12-one[7,15,21-23] **(9ai)**

Compound **9ai** was prepared by the *general procedure 5* from **3ai** or **4ai**. The product (**9ai** from **3ai**, soild, 0.1042 g, 0.44 mmol, 89%, R_f = 0.21 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0760 g, 0.32

mmol, 65%). Alternatively, the product (**9ai** from **4ai**, solid, 0.2214 g, 0.94 mmol, 94%, R_f = 0.21 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0918 g, 0.39 mmol, 39%). m.p. 342–343 °C; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.41 (d, 1H, *J* = 7.8 Hz), 8.23 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.78 (td 1H, *J* = 7.8, 1.2 Hz), 7.52 (d, 1H, *J* = 7.8 Hz), 7.48 (d, 1H, *J* = 7.8 Hz), 7.43 (td, 1H, *J* = 7.5, 0.8 Hz), 7.33 (td, 1H, *J* = 8.1, 0.8 Hz), 7.29 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 159.5, 147.5, 146.0, 135.1, 127.7, 127.2, 126.2, 122.6, 122.1, 121.5, 115.4, 115.1, 112.5; ^{1}H NMR (added a drop of TFA, DMSO-d_6, 600 MHz) δ 8.46 (d, 1H, *J* = 7.8 Hz), 8.29 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.89–7.86 (m, 1H), 7.63 (dd, 2H, *J* = 8.4, 5.2 Hz), 7.53 (t, 1H, *J* = 8.4 Hz), 7.47–7.40 (m, 2H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 150 MHz) δ 158.9, 146.5, 142.1, 136.2, 133.3, 127.9, 127.3, 127.2, 124.6, 123.6, 120.2, 116.0, 115.6, 113.6; MS (EI, 20 eV) *m/z* 235 (100) (M^+); HRMS (EI, sector) calcd for $C_{14}H_9N_3O$: 235.0746. Found: 235.0747.

8-Methylbenzimidazo[2,1-*b*]quinazolin-12-one[7] (9aj)

Compound **9aj** was prepared by the *general procedure 5* from **3aj**. The product (**9aj**, soild, 0.0979 g, 0.39 mmol, 98%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 / 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (brown solid, 0.0746 g, 0.30 mmol, 75%). m.p. 285–286 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.44 (br, 1H), 8.26 (d, 1H, *J* = 8.0 Hz), 8.21 (d, 1H, *J* = 8.0 Hz), 7.76 (td, 1H, *J* = 7.8, 1.3 Hz), 7.51 (d, 1H, *J* = 8.0 Hz), 7.31 (t, 1H, *J* = 7.5 Hz), 7.26 (s, 1H), 7.09 (d, 1H, *J* = 8.0 Hz), 2.44 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.3, 147.7, 135.9, 134.9, 127.1, 125.3, 122.6, 122.4, 115.3, 115.0, 113.3, 21.8; ^{1}H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.27 (dd, 2H, *J* = 9.8, 3.8 Hz), 7.87 (t, 1H, *J* = 8.5 Hz), 7.65 (d, 1H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 7.8 Hz), 7.40 (s, 1H), 7.22 (d, 1H, *J* = 8.5 Hz), 2.44 (s, 3H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 158.5, 146.2, 141.4, 137.6, 136.4, 132.5, 128.0, 125.1, 125.02, 124.99, 120.0, 115.8, 115.7, 113.5, 21.9; MS (EI, 20 eV) *m/z* 249 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{11}N_3O$: 249.0902. Found: 249.0900.

8-Fluorobenzimidazo[2,1-*b*]quinazolin-12-one[23] (9ak)

Compound **9ak** was prepared by the *general procedure 5* from **3ak**. The product (**9ak**, soild, 0.1117 g, 0.44 mmol, 88%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0856 g, 0.34 mmol, 68%). m.p. 339–340 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.68 (br, 1H), 8.33 (dd, 1H, *J* = 8.8, 5.3 Hz), 8.21 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.79 (td, 1H, *J* = 8.0, 1.5 Hz), 7.51 (d, 1H, *J* = 8.5 Hz), 7.35–7.32 (m, 2H), 7.11–7.07 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.8 (d, $^1J_{CF}$ = 237.5 Hz), 159.1, 148.6, 143.5, 140.5, 135.4, 127.4, 125.0, 122.8, 119.8, 115.9 (d, *J* = 11.3 Hz), 114.4, 108.3 (d, *J* = 25.0 Hz), 101.9 (d, *J* = 23.8 Hz); ^{1}H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.36 (dd, 1H, *J* = 8.5, 5.0 Hz), 8.23 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.83–7.79 (m, 1H), 7.55 (d, 1H, *J* = 8.5 Hz), 7.39–7.36 (m, 2H), 7.14–7.10 (m, 1H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 161.1 ($^1J_{CF}$ = 191.1 Hz), 159.0, 148.2, 142.6, 138.8 (*J* = 11.0 Hz), 135.9, 127.7, 124.8, 123.7, 119.8, 116.5 (*J* = 9.0 Hz), 114.9, 109.4 (*J* = 19.0 Hz), 102.0 (*J* = 22.0 Hz); ^{19}F NMR (added a drop of TFA, DMSO-d_6, 375 MHz) δ -115.1; MS (EI, 20 eV) *m/z* 253 (100) (M^+); HRMS (EI, sector) calcd for $C_{14}H_8FN_3O$: 253.0651. Found: 253.0657.

9-Methylbenzimidazo[2,1-*b*]quinazolin-12-one (9bj)

Compound **9bj** was prepared by the *general procedure 5* from **4aj**. The product (**9bj**, soild, 0.0968 g, 0.39 mmol, 97%, R_f = 0.12 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0283 g, 0.11 mmol, 28%). m.p. 316–317 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.45 (br, 1H), 8.23 (s, 1H), 8.20 (d, 1H, *J* = 8.0 Hz), 7.75 (td, 1H, *J* = 7.8, 1.0 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.30 (t, 1H, *J* = 7.5 Hz), 7.23 (d, 1, *J* = 8.0 Hz), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.5, 147.5, 146.2, 135.0, 133.8, 130.8, 127.7, 127.2, 127.0, 122.5, 122.1, 115.6, 115.1, 112.9, 21.7; ^{1}H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.26 (dd, 2H, *J* = 6.3, 1.3 Hz), 7.86 (t, 1H, *J* = 8.3 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.48–7.42 (m, 2H), 7.31 (d, 1H, *J* = 8.0 Hz), 2.47 (s, 3H); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 158.8, 146.3, 142.2, 136.1, 133.1, 130.9, 128.0, 127.8, 127.3, 124.4, 120.2, 116.0, 115.4, 113.0, 21.7; MS (EI, 20 eV) *m/z* 249 (100) (M^+); HRMS (EI, sector) calcd for $C_{15}H_{11}N_3O$: 249.0902. Found: 249.0903.

9-Fluorobenzimidazo[2,1-*b*]quinazolin-12-one (9bk)

Compound **9bk** was prepared by the *general procedure 5* from **4bk**. The product (**9bk**, soild, 0.1152 g, 0.45 mmol, 91%, R_f = 0.23 ($CHCl_3$ / MeOH = 98 : 2)) was purified by flash column chromatography (CH_2Cl_2 / MeOH = 98 : 2) then recrystallized from $CHCl_3$ / EtOH (about 1 : 1 (*v*/*v*)) (white solid, 0.0668 g, 0.26 mmol, 53%). m.p. 333–334 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.62 (br, 1H), 8.20 (dd, 1H, *J* = 8.0, 1.5 Hz), 8.12 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.80–7.77 (m, 1H), 7.51–7.48 (m, 2H), 7.33–7.26 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.4, 157.4 ($^1J_{CF}$ = 235 Hz), 148.0, 144.2, 135.5, 127.4, 122.6, 120.2, 115.4, 113.1 (d, *J* = 23.8 Hz), 102.6 (d, *J* = 30 Hz); ^{1}H NMR (added a drop of TFA, DMSO-d_6, 500 MHz) δ 8.25 (dd, 1H, *J* = 8.0, 1.0 Hz), 8.17 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.86–7.82 (m, 1H), 7.59 (dd, 2H, *J* = 8.8, 4.3 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 7.33 (td, 1H, *J* = 7.6, 2.0 Hz); ^{13}C NMR (added a drop of TFA, DMSO-d_6, 125 MHz) δ 159.1, 158.7 ($^1J_{CF}$ = 190.1 Hz), 147.4, 142.2, 136.4, 131.9, 128.04, 127.98, 124.3, 119.8, 115.3 (*J* = 8.0 Hz), 115.1, 114.3 (*J* = 19.0 Hz), 103.5 (*J* = 23.0 Hz); ^{19}F NMR (added a drop of TFA, DMSO-d_6, 375 MHz) δ -119.0; MS (EI, 20 eV) *m/z* 253 (100) (M^+); HRMS (EI, sector) calcd for $C_{14}H_8FN_3O$: 253.0651. Found: 253.0656.

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