Exploration of the Structural Space in 4(3*H*)-Quinazolinone Antibacterials

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Experiment procedures and characterization of synthesized compounds

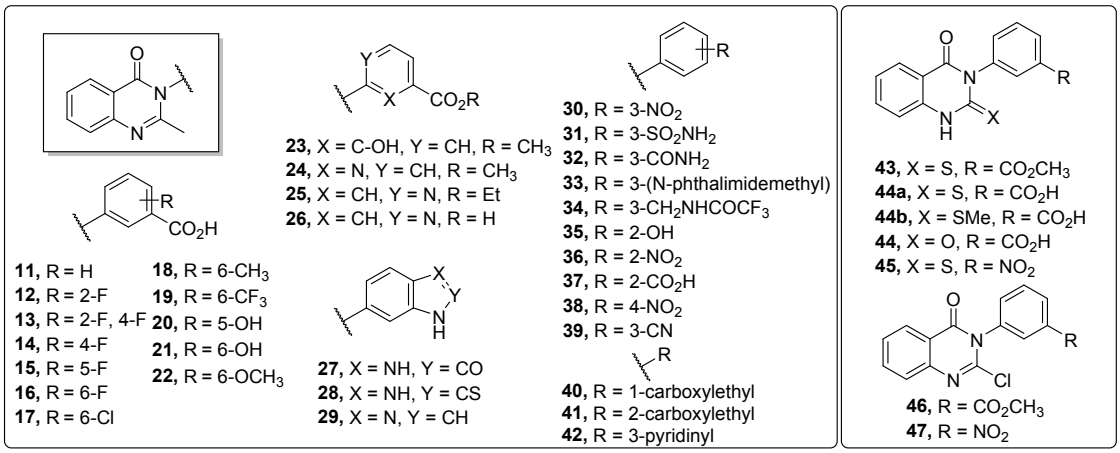


Figure S1. Chemical structures of synthesized intermediates.

2-Fluoropyridine containing compounds **61** and **65** were made by $ZnCl_2$-catalyzed condensation of **11** and respective aldehydes.[1] The retro-amides **89**–**91** were obtained using **111** and the respective carboxylic acids as starting material, in combination with coupling agents EDC with HOBt[2] or HATU[3] at rt for 8–12 h. The urea derivatives **92**–**93** were synthesized in a two-step reaction by modification of a previously published protocol,[3] forming a carbamate first, followed by addition of the amine resulting in urea formation. Analog **95** was obtained by acylation of **94** in acetic anhydride. The protective groups in **80**, **82**, **97** and **118** were removed by aqueous LiOH or NaOH. The pyridine N-oxide analog **106** was obtained by oxidation of **105** with *m*-CPBA. The azide-containing analog **108** was obtained by Sandmeyer reaction of aniline **111** with $NaNO_2$ followed by reaction with NaN_3. The analogs with saturated linkers (**114** and **115**) were obtained by catalytic hydrogenation from the respective alkenyl derivatives (**1** and **115a**).[4] Compounds **98**, **104**[4], **121**, **122**, **128** and **129** were synthesized from their respective nitro precursors, which were reduced to the corresponding anilines using tin(II) chloride in ethanol in acidic conditions under reflux.[4]

3-(3-Carboxy-2-fluorophenyl)-2-methylquinazolin-4(3*H*)-one (12). The compound was synthesized according to the general procedure **A** from compound **3**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water followed by diethyl ether giving the title compound (204 mg, 55%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.54 (br s, 1H), 8.13 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 7.4 Hz, 1H), 7.91–7.87 (m, 2H), 7.70 (d, J = 8.1 Hz, 1H), 7.58–7.49 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.3(d, J_{CF} = 2.3 Hz, 1C), 160.7, 156.2 (d, J_{CF} = 261.2 Hz, 1C), 153.8, 147.2, 135.2, 134.9, 133.1, 127.0, 126.9, 126.4, 126.2 (d, J_{CF} = 14.3 Hz, 1C), 125.2 (d, J_{CF} = 5.1 Hz, 1C), 120.8 (d, J_{CF} = 7.9 Hz, 1C), 119.9, 23.4.

3-(3-Carboxy-2,4-difluorophenyl)-2-methylquinazolin-4(3*H*)-one (13). The compound was synthesized according to the general procedure **A** from compound **3**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water followed by diethyl ether giving the title compound (206 mg,

53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.27 (br s, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.91–7.87 (m, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.0 Hz, 1H), 7.48 (t, J = 9.0 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 160.7, 159.4 (d, J_{CF} = 125.3 Hz, 1C), 159.3 (d, J_{CF} = 255.6 Hz, 1C), 153.8, 147.1, 135.2, 133.5 (d, J_{CF} = 10.5 Hz, 1C), 127.0, 126.9, 126.4, 121.9 (dd, J_{CF} = 14.5 Hz, 3.9 Hz), 119.8, 113.4 (dd, J_{CF} = 23.6 Hz, 4.0 Hz, 1C), 113.3, 23.6.

3-(3-Carboxy-4-fluorophenyl)-2-methylquinazolin-4(3*H*)-one (14). The compound was synthesized according to the general procedure **A** from compound **3**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water giving the title compound (209 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.51 (br s, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.98 (dd, J = 6.4 Hz, 2.6 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.79–7.75 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.56–7.50 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.3 (d, J_{CF} = 2.9 Hz, 1C), 161.5, 160.8 (d, J_{CF} = 259.0 Hz, 1C), 154.2, 147.3, 134.9 (d, J_{CF} = 9.5 Hz, 1C), 134.7, 133.9 (d, J_{CF} = 3.5 Hz, 1C), 132.2, 126.7, 126.5, 126.3, 120.6 (d, J_{CF} = 11.7 Hz, 1C), 120.4, 118.4 (d, J_{CF} = 23.9 Hz), 24.1.

3-(5-Carboxy-3-fluorophenyl)-2-methylquinazolin-4(3*H*)-one (15). The compound was synthesized according to the general procedure **B** from compound **3**. The concentrated mixture was purified by preparative TLC using hexanes:EtOAc:acetic acid (70:30:1) to give the title compound (138 mg, 37%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.62 (br s, 1H), 8.10 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.90 (t, J = 1.2 Hz, 1H), 7.87–7.81 (m, 2H), 7.78 (dt, J = 9.0 Hz, 2.1 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 8.0 Hz, 7.1 Hz, 1.0 Hz, 1H), 2.16 (s, 3H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 162.1 (d, J_{CF} = 246.4 Hz, 1C), 161.3, 153.8, 149.6, 147.3, 139.6 (d, J_{CF} = 10.3 Hz, 1C), 136.2, 134.8, 126.7, 126.5, 126.0 (d, J_{CF} = 3.0 Hz, 1C), 120.6, 120.4, 166.6 (d, J_{CF} = 22.7 Hz, 1C), 24.0.

3-(5-Carboxy-2-chlorophenyl)-2-methylquinazolin-4(3*H*)-one (17). Compound **3** (179 mg, 1.11 mmol) and 3-amino-4-chlorobenzoic acid (200 mg, 1.17 mmol) were added to 10 mL of toluene in a 50-mL round-bottom flask. The Dean-Stark apparatus was used to isolate water from the solution. The solution was refluxed for 12 h. After solution was cooled down, hexanes were added, which resulted in precipitation. The resulting suspension was then filtered and the solid was washed with hexanes to give the title compound (109 mg, 31%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 8.26 (br s, 1H), 8.19–8.02 (m, 2H), 7.99–7.80 (m, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 161.1, 153.9, 147.7, 136.6, 135.9, 135.5, 132.2, 132.1, 132.0, 131.1, 127.33, 127.29, 126.9, 120.6, 23.7.

3-(3-Carboxy-6-methylphenyl)-2-methylquinazolin-4(3*H*)-one (18). The compound was synthesized according to the general procedure **A** from compound **3**. The resulting suspension was filtered and washed with water (3×) and EtOAc to give the title compound (121 mg, 33%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.13 (d, J = 7.7 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.96 (s, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 2.10 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 160.7, 153.9, 147.3, 140.3, 136.9, 134.7, 131.3, 130.6, 130.0, 129.5, 126.7, 126.5, 126.3, 120.2, 23.4, 17.0.

3-(5-Carboxy-2-trifluoromethylphenyl)-2-methylquinazolin-4(3*H*)-one (19). Compound **3** (150 mg, 0.93 mmol) and 3-amino-4-(trifluoromethyl)benzoic acid (200 mg, 0.93 mmol)

were dissolved in toluene (10 mL) and the mixture was stirred for 2 days under reflux using a Dean-Stark apparatus. A precipitate was formed and the solid was isolated by filtration, washed with hot toluene giving title compound (272 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11 (s, 3H), 7.60–7.51 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.92–7.85 (m, 1H), 8.11 (dd, J = 1.2, 8.0 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 8.29 (br d, J = 8.2 Hz, 1H), 8.37 (s, 1H), 13.78 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 161.9, 154.1, 147.6, 137.1, 136.4, 135.5, 132.8, 131.4, 130.2, 128.80, 128.76, 127.3, 126.8, 125.9 (q, J_{CF} = 274.1 Hz, 1C), 120.4, 24.0. ^{19}F NMR (376 MHz, DMSO-d_6) -60.66 (s, 3F).

3-(5-Carboxy-3-hydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (20). The compound was synthesized according to the general procedure **A** from compound **3**. The mixture was cooled to rt and residue solvent was removed *in vacuo* to give yellow oil. The oil was triturated with a mixture of methanol and EtOAc (methanol:EtOAc = 1:9), which resulted in a precipitate. The precipitate was filtered to give title compound (245 mg, 31%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (br s, 1H), 10.26 (s, 1H), 8.09 (dd, J = 1.2, 8.0 Hz, 1H), 7.83 (ddd, J = 1.6 Hz, 7.2 Hz, 8.1 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.51 (5-line multiplet, ω= 15.1 Hz, assigned as a ddd, J = 8, 7, 1.1 Hz, 1H), 7.48 (dd, J = 1.4, 2.4 Hz, 1H), 7.40 (t, J = 1.6 Hz, 1H), 7.09 (t, J = 2.1 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 161.3, 158.4, 154.1, 147.4, 139.1, 134.6, 133.2, 126.7, 126.4, 126.3, 120.5, 120.02, 119.99, 116.5, 23.9.

3-(5-Carboxy-2-hydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (21). The compound was synthesized according to the general procedure **A** from compound **3**. The resulting precipitate was filtered and washed with water (3×) and EtOAc (2×) to give a pink precipitate, which was sequentially triturated with cold methanol (5 mL) and hot water (20 mL) to give title compound (308 mg, 39%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 10.98 (s, 1H), 8.10 (dd, J = 1.2, 8.0 Hz, 1H), 7.95 (dd, J = 2.2, 8.6 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.85 (ddd, J = 1.5, 7.2, 8.1 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.56–7.48 (m, 1H), 7.14 (d, J = 8.6 Hz, 1H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.2, 161.7, 157.7, 155.4, 148.1, 135.3, 132.8, 132.3, 127.3, 127.1, 127.0, 125.3, 123.1, 121.2, 117.3, 23.8.

3-(5-Carboxy-2-methoxyphenyl)-2-methylquinazolin-4(3*H*)-one (22). The compound was synthesized according to the general procedure **A** from compound **3**. The resulting precipitate was filtered and washed with water (5 mL, 3×) and EtOAc (5 mL, 3×) to give off-white precipitate, which was sequentially triturated by hot water (20 mL) to give crude product without purification.

3-(2-Hydroxy-5-(methoxycarbonyl)phenyl)-2-methylquinazolin-4(3*H*)-one (23). The compound was synthesized according to the general procedure **B** from compound **3**. The solution was concentrated *in vacuo* to give brown oil before being taken up by EtOAc (25 mL). The organic layer was washed with $NaHCO_3$ solution (2×), brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give brown oil, which was further purified by silica gel column chromatography. (EtOAc;hexanes = 15;85) to give the title compound (370 mg, 40%) as a yellow crystal. ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (dd, J = 1.1, 8.0 Hz, 1H), 7.88 (ddd, J = 8.2, 7.2, 1.5 Hz, 1H), 7.74–7.67 (m, 3H), 7.88 (5-line multiplet, ω= 15.2 Hz, assigned as a ddd, J = 8, 7, 1.1 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 166.2, 162.0, 155.5, 153.0, 147.2, 134.8, 132.5, 129.5, 128.7, 126.6, 126.4, 126.0, 120.9, 120.2, 117.3, 51.5, 21.7.

3-(6-(Methoxycarbonyl)pyridin-2-yl)-2-methylquinazolin-4(3*H*)-one (24). The compound was synthesized according to the general procedure **B** from compound **3**. The mixture was concentrated *in vacuo* to give a brown oil. The oil was dissolved in EtOAc and washed with 5% citric acid solution (2×), saturated Na_2CO_3 solution (2×) and brine (2×). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a yellow oil, which was further purified with silica gel column chromatography (EtOAc:hexanes = 30:70) to give the title compound (140 mg, 15%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.7 Hz, 1H), 8.24 (br d, *J* = 7.8 Hz, 1H), 8.11 (t, *J* = 7.8 Hz, 1H), 7.82–7.72 (m, 1 H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 4.01 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 162.4, 153.0, 151.2, 148.8, 147.7, 140.3, 135.2, 127.6, 127.2, 127.10, 127.09, 126.1, 121.0, 53.5, 24.1.

3-(4-(Ethoxycarbonyl)pyridin-2-yl)-2-methylquinazolin-4(3*H*)-one (25). To a 15 mL tube were compound **3** (529 mg, 3.28 mmol) and 2-amino-isonicotinic acid ethyl ester (600 mg, 3.61 mmol) dissolved in 5 mL anhydrous DMF. The tube was sealed, and the mixture was heated up to 120 °C with stirring on for 8 h. The mixture was poured into cold water (20 mL) and washed with EtOAc (10 mL, 3×). The organic layers were combined, washed with excessive water (50 mL, 2×) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the crude product without purification. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{16}N_3O_3$, 310.1186; found: 310.1162.

3-(4-Carboxypyridin-2-yl)-2-methylquinazolin-4(3*H*)-one (26). To a 25 mL single-neck flask was the crude compound **25** dissolved in a mixture of ethanol and water (EtOH:H_2O = 4:1, 10 mL), followed by lithium hydroxide (158 mg, 6.59 mmol). The resulting mixture was stirred for 2 h at rt. The mixture was concentrated *in vacuo* before being taken up by EtOAc (10 mL). The solution was then washed with 1N HCl (aq., 10 mL) and brine (10 mL). Organic layer was collected, washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to produce pink powder as desired product (95 mg, 8%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.91 (br s,1 H), 8.86 (dd, *J* = 0.7, 5.1 Hz, 1H), 8.15–8.06 (m, 2H), 8.00 (dd, *J* = 1.5, 5.1 Hz, 1H), 7.90–7.82 (m, 1H), 7.72–7.63 (m, 1H), 7.57–7.49 (m, 1H), 2.11 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.0, 162.0, 154.0, 152.4, 151.6, 147.9, 142.1, 135.7, 127.48, 127.47, 127.0, 124.6, 124.2, 121.0, 23.9.

2-Methyl-3-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4(3*H*)-one (27). The compound was synthesized according to the general procedure **A** from compound **3**. The concentrated mixture was taken up with brine and washed with EtOAc (3×). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure giving the title compound (305 mg, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (d, *J* = 4.3 Hz, 2H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.94 (dd, *J* = 8.1 Hz, 1.19 Hz, 1H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 155.5, 155.2, 147.4, 134.4, 130.6, 130.2, 129.9, 126.6, 126.3, 126.2, 120.6, 120.5, 108.7 (2C), 24.0.

2-Methyl-3-(2-thioxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4(3*H*)-one (28). The compound was synthesized according to the general procedure **A** from compound **3**. The concentrated reaction mixture was diluted in brine and washed with EtOAc (15 mL, 3×). The organic layers were collected, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting oil was triturated with water (10 mL). The precipitate

was isolated by filtration, washed with water, followed by hexanes and a mixture of EtOAc:hexanes (1:10) giving the title compound (199 mg, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 7.8 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.28–7.26 (m, 2H), 7.11 (d, J = 8.5 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.5, 169.7, 161.6, 154.9, 147.4, 134.5, 133.6, 133.1, 132.0, 126.6, 126.3, 122.1, 120.6, 109.9, 24.0.

3-(1*H*-Benzo[*d*]imidazol-6-yl)-2-methylquinazolin-4(3*H*)-one (29). The compound was synthesized according to the general procedure **A** from compound **3**. Water (20 mL) was poured in the concentrated mixture and solid $NaHCO_3$ was added stepwise in the mixture until pH ≈ 8. The mixture was washed with DCM (10 mL, 3×) and the organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure giving the title compound (312 mg, 91%) without purification.

2-Methyl-3-(3-sulfamoylphenyl)quinazolin-4(3*H*)-one (31). The title compound was synthesized according to the general procedure **B** from compound **3**. The resulting suspension was filtered and the solid was washed with water (3×) to give the crude product without any purification.

3-(3-Carbamoylphenyl)-2-methylquinazolin-4(3*H*)-one (32). The compound was synthesized according to the general procedure **A** from compound **3**. The reaction mixture was cooled to rt to give a pale-white precipitation. The precipitation was filtered and washed with water (3×) to produce the title compound (850 mg, 98%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 7.8 Hz, 1H), 8.07 (br s, 1H), 8.02 (d, J = 6.8 Hz, 1H), 7.90 (br s, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.73–7.61 (m, 3H), 7.59–7.48 (m, 2H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 161.8, 154.7, 147.8, 138.3, 136.3, 135.2, 131.8, 130.1, 128.5, 128.1, 127.2, 127.0, 126.8, 120.9, 24.6.

3-(3-((1,3-Dioxoisoindolin-2-yl)methyl)phenyl)-2-methylquinazolin-4(3*H*)-one (33). The compound was synthesized according to the general procedure **B** from compound **3**. Water was poured in the concentrated mixture and solid $NaHCO_3$ was added stepwise in the mixture until pH ≈ 8. The mixture was washed with EtOAc and the organic layers were collected together, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure giving the title compound (1.37 g, 24%) without purification.

2,2,2-Trifluoro-N-(3-nitrobenzyl)acetamide (34a). (3-Nitrophenyl)methanamine hydrochloride (1.00 g, 5.30 mmol) was suspended in a solution of trimethylamine (3.70 mL, 2.68 g, 26.5 mmol) in dichloromethanse (20 mL). Trifluoroacetic anhydride (1.10 mL, 1.67 g, 7.95 mmol) was added dropwise to the solution and the reaction was stirred at rt for 30 min, until it became clear. The mixture was washed with 1 N HCl (aq.), water (3×) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure giving the title compound (1.03 g, 79%) as a light-yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20–8.17 (m, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 4.57 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 159.2 (d, J_{CF} = 37.0 Hz, 1C), 149.8, 140.9, 135.0, 131.0, 123.6, 123.5, 118.0 (q, J_{CF} = 287.3 Hz, 1C), 43.1.

***N*-(3-Aminobenzyl)-2,2,2-trifluoroacetamide (34b).** A solution of **34a** (890 mg, 3.59 mmol) in anhydrous THF (10 mL) was stirred in a 25-mL round-bottom flask. The system was purged with nitrogen before 10% palladium/carbon (89 mg) was added. The resulting

suspension was flushed with hydrogen and the mixture was stirred at rt for 2 hours under a positive hydrogen pressure in a balloon. The reaction was monitored by analytical TLC, and on completion, the mixture was filtered over celite. The filtrate was dried *in vacuo* and purified by silica-gel column chromatography (hexanes:EtOAc = 85:15) giving the desired title compound (610 mg, 78%) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 (t, J = 7.8 Hz, 1H), 6.66–6.60 (m, 3H), 4.35 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 158.9 (q, J_{CF} = 36.8 Hz, 1C), 149.2, 139.3, 130.4, 118.3, 117.7 (q, J_{CF} = 286.6 Hz, 1C), 115.8, 115.6, 44.3.

2-Methyl-3-((2,2,2-trifluoroacetamido)methyl)-quinazolin-4(3*H*)-one (34). The compound was synthesized according to the general procedure **B** from compounds **34b** and **3**. The mixture was purified by silica-gel column chromatography (hexanes:EtOAc = 50:50) to produce giving the title compound (497 mg, 59%) as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (t, J = 5.6 Hz, 1H) , 8.10 (d, J = 7.9 Hz, 1H), 7.84 (t, J = 6.9 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.42–7.37 (m, 3H), 4.48 (d, J = 5.9 Hz, 2H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 156.5 (q, J_{CF} = 36.4 Hz, 1C), 154.3, 147.3, 139.2, 138.0, 134.6, 129.8, 127.8, 127.5, 127.3, 126.7, 126.5, 126.3, 120.5, 116.0 (q, J_{CF} = 288.1 Hz, 1C), 42.2, 24.0.

2-Methyl-3-(2-nitrophenyl)quinazolin-4(3*H*)-one (36). The compound was synthesized according to the general procedure **A** from compound **3**. Water was poured in the concentrated mixture, which resulted in a precipitate. The precipitate was filtered and washed with water to give the title compound (190 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (dd, J = 1.2, 8.1 Hz, 1H), 8.08 (dd, J = 1.2, 8.1 Hz, 1H), 8.04–7.97 (m, 1H), 7.94–7.81 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H), 7.59–7.50 (m, 1H), 2.24 (s, 3H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 154.1, 147.7, 146.0, 136.0, 135.7, 131.9, 131.6, 131.2, 127.4, 127.3, 126.8, 126.4, 120.2, 24.2.

3-(2-Carboxyphenyl)-2-methylquinazolin-4(3*H*)-one (37). The compound was synthesized according to the general procedure **A** from compound **3**. Water was poured in the concentrated mixture, which resulted in a precipitate. The precipitate was filtered and washed with water to give the title compound (0.41 g, 73%) without purification.

2-Methyl-3-(4-nitrophenyl)quinazolin-4(3*H*)-one (38). The compound was synthesized according to the general procedure **A** from compound **3**. The residue solvent was removed to give orange oil, which was triturated with 10 mL of EtOAc to give a white precipitate. The precipitate was filtered and washed with EtOAc (5 mL). The brown filtrate was washed with ammonia solution, brine and dried over anhydrous Na_2SO_4. The filtrate was then concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc:hexanes = 40:60) to give the title compound (0.98 g, 56%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45–8.43 (m, 1H), 8.43–8.41 (m, 1H), 8.10 (d, J = 1.1 Hz, 1H), 7.91–7.81 (m, 3H), 7.69 (dd, J = 0.5, 8.1 Hz, 1H), 7.58–7.50 (m, 1H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 154.1, 148.3, 148.0, 144.4, 135.5, 131.1, 127.4, 127.3, 127.0, 125.5, 121.0, 24.7.

3-(3-Cyanophenyl)-2-methylquinazolin-4(3*H*)-one (39) The compound was synthesized according to the general procedure **A** from compound **3**. Water was poured in the concentrated mixture, which resulted in a precipitate. The precipitate was filtered and washed with water to give the title compound (232 mg, 46%) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (dd, J = 1.1, 8.0 Hz, 1H), 7.93 (td, J = 1.6, 7.2 Hz, 1H), 7.90–7.83 (m,

2H), 7.79 (dt, *J* = 0.6, 7.6 Hz, 1H), 7.75 (td, *J* = 1.9, 8.2 Hz, 1H), 7.68 (dd, *J* = 0.4, 8.2 Hz, 1H), 7.58–7.51 (m, 1H) 2.27 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 161.9, 155.3, 146.0, 138.2, 135.1, 133.3, 133.1, 132.2, 131.0, 127.1, 126.5, 125.4, 120.1, 117.2, 113.8, 22.5.

3-(1-Carboxyethyl)-2-methylquinazolin-4(3*H*)-one (40) The compound was synthesized according to the general procedure **B** from compound **3**. The reaction solution was concentrated *in vacuo* to give dark brown oil. EtOAc (40 mL) was added to the oil with stirring on for 20 mins to give a precipitate. The precipitate was then filtered and washed with EtOAc (5 mL, 3×) to give the title compound (2.20 g, 31%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 8.06 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.86–7.75 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 5.14 (q, *J* = 6.8 Hz, 1H), 2.62 (s, 3H), 1.57 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 161.1, 155.2, 147.4, 135.0, 127.0, 126.9, 126.5, 120.7, 55.1, 23.8, 14.8.

3-(2-Carboxyethyl)-2-methylquinazolin-4(3*H*)-one (41) The compound was synthesized according to the general procedure **A** from compound **3**. The reaction solution was concentrated under reduced pressure until a precipitate was formed. The precipitate was then filtered and washed with water (5 mL, 3×) to give the title compound (0.49 g, 68%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.09 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.83–7.74 (m, 1H), 7.58 (d, *J* = 7.7 Hz ,1H), 7.52–7.44 (m, 1H), 4.29–4.19 (m, 2H), 2.75–2.66 (m, 2H), 2.64 (s, 3H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 161.6, 155.5, 147.5, 134.8, 126.9, 126.7, 126.5, 120.4, 40.9, 32.6, 23.3.

2-Methyl-3-(pyridin-3-yl)quinazolin-4(3*H*)-one (42). The compound was synthesized according to the general procedure **A** from compound **3**. The mixture was concentrated *in vacuo* to give a brown oil. The oil was purified by silica-gel column chromatography (DCM:methanol = 99:1) to give the title compound (126 mg, 17%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 1.5, 4.8 Hz, 1H), 8.56 (d, *J* = 2.2 Hz, 1H), 8.23 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.82–7.73 (m, 1H), 7.71–7.62 (m, 2H), 7.52 (ddd, *J* = 0.6, 4.8, 8.1 Hz, 1H), 7.50–7.44 (m, 1H), 2.23 (s, 3H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82–8.65 (m, 2H), 8.11 (dd, *J* = 1.2, 7.9 Hz, 1H), 8.02 (td, *J* = 1.7, 8.1 Hz, 1H), 7.92–7.81 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.59–7.50 (m, 1H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 154.7, 150.3, 149.7, 147.5, 137.2, 135.3, 135.1, 127.1, 127.0, 126.8, 125.0, 120.7, 24.6.

3-(3-Methoxycarbonylphenyl)-2-thiocarbonylquinazolin-4(1*H*)-one (43). The title compound was synthesized according to the general procedure **E** from **2** (1.86 g, 83%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.09 (s, 1H), 7.96 (dd, *J* = 7.3, 22.1 Hz, 2H), 7.90 (s, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.70–7.52 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.1 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.6, 166.4, 160.6, 140.5, 140.3, 136.3, 134.9, 131.2, 130.8, 130.2, 129.6, 128.1, 125.1, 117.0, 116.4, 53.0.

3-(3-Carboxyphenyl)-2-thiocarbonylquinazolin-4(1*H*)-one (44a). The compound was synthesized according to the general procedure from **2** (0.93 g, 63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (br s, 2H), 8.02–7.93 (m, 2H), 7.87 (t, *J* = 1.6 Hz, 1H), 7.84–7.75 (m, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.59–7.54 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.40–7.32 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.4, 167.2, 160.4, 140.10, 140.06, 136.1, 134.2, 132.2, 130.7, 129.7, 129.5, 127.9, 124.9, 116.8, 116.2.

3-(3-Carboxyphenyl)-2-(methylthio)quinazolin-4(1*H*)-one (44b). Compound **44a** (300 mg, 1.01 mmol) was added into 10 mL 1M NaOH water solution with stirring on at rt. The solution of iodomethane (286 mg, 2.01 mmol, 125 μL) in 10 mL methanol was then added slowly by injection. After 1 h stirring, 15 mL 1N HCl (aq.) was added dropwise to the solution until pH = 4. The resulting precipitate was filtered and washed with water to give the title compound (331 mg, 100%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 8.12 (td, J = 1.5, 7.5 Hz, 1H), 8.09 (dd, J = 1.2, 7.9 Hz, 1H), 8.01 (t, J = 1.6 Hz, 1H), 7.88–7.80 (m, 1H), 7.79–7.67 (m, 2H), 7.64 (d, J = 7.7 Hz, 1H), 7.52–7.44 (m, 1 H). The peak of methyl group was overlapped by solvent residual signal at around 2.50 ppm. ^{1}H NMR (400 MHz, Acetone-d_6) 8.25–8.21 (m, 1H), 8.17–8.10 (m, 2H), 7.82 (ddd, J = 1.6, 7.2, 8.2 Hz, 1H), 7.79–7.73 (m, 2H), 7.64 (qd, J = 0.53, 8.2 Hz, 1H), 7.46 (ddd, J = 1.1, 7.1, 8.0 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.9, 161.2, 158.0, 147.8, 136.8, 135.4, 134.5, 132.7, 131.1, 130.9, 130.4, 127.1, 126.6, 126.4, 120.0, 15.5. ^{13}C NMR (101 MHz, Acetone-d_6) δ 165.8, 161.0, 157.8, 147.9, 136.9, 134.6, 134.2, 132.1, 130.9, 130.8, 129.7, 126.8, 126.3, 125.7, 120.0, 14.7.

3(3-Carboxyphenyl)-2,4(*1H,3H*)-quinazolinedione (44). To a 5 mL single-neck flask were **44b** (50 mg, 0.16 mmol) and *m*-CBPA (45 mg, 0.32 mmol) dissolved in DCM (10 mL). The mixture was stirred at rt for 8 h. The mixture was then quenched by $Na_2S_2O_3$ solution to give a white precipitate. The precipitate was filtered and washed with DCM (2 mL, 3×) to give the title compound (34 mg, 75%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) 13.14 (s, 1H), 11.60 (s, 1H), 8.02–7.97 (m, 1H), 7.95 (dd, J = 1.1, 8.1 Hz, 1H), 7.92–7.87 (m, 1H), 7.71 (5-line multiplet, ω= 15.5 Hz, assigned as a ddd, J = 8, 7, 1.4 Hz, 1H), 7.66–7.58 (m, 2H), 7.29–7.20 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 162.7, 150.6, 140.3, 136.5, 135.7, 134.2, 132.1, 130.7, 129.6, 129.5, 128.0, 123.0, 115.7, 114.8.

3-(3-Nitrophenyl)-2-thiocarbonylquinazolin-4(1*H*)-one (45). The compound was synthesized according to the general procedure **E** from **2** (3.02 g, 91%) as a white solid. ^{1}H NMR (400 MHz, DMSO) 13.18 (s,1H), 8.34 (t, J = 1.9 Hz, 1H), 8.30 (ddd, J = 1.5, 2.3, 7.8 Hz, 1H), 7.98 (dd, J = 1.2, 8.0 Hz, 1H), 7.86–7.76 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.42–7.34 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.2, 160.4, 148.7, 141.0, 140.1, 137.0, 136.2, 130.8, 127.9, 125.2, 125.0, 123.8, 116.8, 116.3.

2-Chloro-3-(3-methoxycarbonylphenyl)quinazolin-4(3*H*)-one (46) The compound was synthesized according to the general procedure **F** from anthranilic acid to give the title compound (89 mg, 88%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (ddd, J = 0.4, 1.5, 8.0 Hz, 1H), 8.22 (td, J = 1.4, 7.8 Hz, 1H), 8.00 (t, J = 1.7 Hz, 1H), 7.83 (ddd, J = 1.6, 7.2, 8.2 Hz, 1H), 7.72 (ddd, J = 0.5, 1.1, 8.2 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.55 (ddd, J = 1.2, 7.2, 8.0 Hz, 1H), 7.51 (ddd, J = 1.1, 2.2, 7.9 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.7, 162.3, 150.2, 139.9, 136.2, 135.3, 134.2, 130.4, 130.1, 129.4, 128.9, 127.6, 122.6, 115.3, 114.4, 52.3.

2-Chloro-3-(3-nitrophenyl)quinazolin-4(3*H*)-one (47). The compound was synthesized according to the general procedure **F** from **2** (6.50 g, 72%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (t, J = 2.0 Hz, 1H), 8.41 (ddd, J = 1.0, 2.3, 8.3 Hz, 1H), 8.14 (ddd, J = 0.4, 1.5, 7.9 Hz, 1H), 8.07 (ddd, J = 1.0, 1.9, 7.9 Hz, 1H), 7.94 (ddd, J = 1.5, 7.2, 8.2 Hz, 1H), 7.90 (t, J = 8.2 Hz, 1H), 7.74 (ddd, J = 0.6, 1.2, 8.2 Hz, 1H), 7.63 (ddd, J = 1.1, 7.3, 7.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 149.0, 147.1, 143.8, 139.4, 136.6, 136.2, 131.6, 128.4, 127.6, 127.4, 125.14, 125.07, 121.3.

(*E*)-3-(3-Carboxyphenyl)-2-(2-cyclopropylvinyl)quinazolin-4(3*H*)-one (48). The compound was prepared according to general procedure **C** from compound **11.** The crude product was purified by silica gel column chromatography (EtOAc:hexanes = 50:50) and triturated by EtOAc (5 mL) to give the title compound (53 mg, 9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 13.31 (s, 1H), 8.11 (td, J= 1.5, 7.6 Hz, 1H), 8.08 (dd, J= 1.2, 8.0 Hz, 1H), 7.94 (t, J= 1.6 Hz, 1H), 7.88–7.78 (m, 1H), 7.74 (t, J= 7.7 Hz, 1H), 7.70–7.62 (m, 2H), 7.52–7.42 (m, 1H), 6.61 (dd, J= 10.4, 14.8 Hz, 1H), 5.73 (d, J= 14.8 Hz, 1H), 1.59–1.40 (m, 1H), 0.94–0.74 (m, 2H), 0.70–0.56 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 161.9, 151.3, 149.9, 148,0, 138.0, 135.2, 133.9, 132.8, 130.6, 130.4, 130.3, 127.3, 126.8, 126.5, 120.7, 119.6, 15.7, 9.0. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{20}H_{17}N_2O_3$, 333.1234; found, 333.1236.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(thiazol-2-yl)vinyl)quinazolin-4(3*H*)-one (49). The compound was synthesized according to the general procedure **D** from compound **11**. Water was added to the crude reaction mixture, which resulted in a precipitate. The precipitate was separated by filtration, washed with water giving the title compound (139 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (br s, 1H), 8.14 (d, J= 7.0 Hz, 2H), 8.07 (s, 1H), 8.00 (d, J= 15.2 Hz, 1H), 7.93–7.89 (m, 2H), 7.83–7.73 (m, 4H), 7.57 (t, J= 7.6 Hz, 1H), 6.65 (d, J= 15.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 162.9, 161.3, 150.2, 147.2, 144.8, 137.2, 134.9, 133.5, 132.4, 130.2 (2C), 130.00, 129.98, 127.4, 127.1, 126.5, 123.4, 123.0, 120.9. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{20}H_{14}N_3O_3S$, 376.0750; found, 376.0751.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(thiazol-5-yl)vinyl)quinazolin-4(3*H*)-one (50). The compound was synthesized according to the general procedure **D** from compound **11**. Water was added in the crude reaction mixture and precipitation occurred. The precipitate was separated by filtration, washed with water giving compound giving the title compound (71 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (br s, 1H), 9.03 (s, 1H), 8.22–8.04 (m, 5H), 7.91–7.87 (m, 1H), 7.81–7.68 (m, 3H), 7.56–7.54 (m, 1H), 6.01 (d, J= 15.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 161.2, 155.7, 150.4, 147.3, 146.3, 137.2, 135.5, 134.9, 133.5, 132.4, 130.1 (2C), 130.0, 128.9, 127.2, 126.8, 126.5, 122.1, 120.7. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{20}H_{14}N_3O_3S$, 376.0750; found, 376.0757.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(thiophen-3-yl)vinyl)quinazolin-4(3*H*)-one (51). The compound was synthesized according to the general procedure **C** from compound **11**. The crude reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (DCM:methanol:acetic acid = 97:2:1 to 94:5:1) giving the title compound (39 mg, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (br s, 1H), 8.13–8.11 (m, 2H), 8.00 (s, 1H), 7.93–7.85 (m, 3H), 7.77–7.71 (m, 3H), 7.54–7.51 (m, 2H), 7.02 (d, J= 4.9 Hz, 1H), 6.12 (d, J= 15.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 161.4, 151.5, 147.5, 137.9, 137.3, 134.8, 133.4, 133.3, 132.5, 130.0 (2C), 129.9, 128.6, 128.0, 127.1, 126.5 (2C), 124.9, 120.5, 119.3. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{21}H_{15}N_2O_3S$, 375.0798; found, 375.0786.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(thiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (52). The compound was synthesized according to the general procedure **C** from compound **11**. Water was added to the crude reaction mixture, which resulted in a precipitate. The precipitate was separated by filtration, washed with water giving the title compound (35 mg, 26%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (br s. 1H), 8.14–8.12 (m, 2H), 8.06 (d, J= 15.3 Hz, 1H), 8.02 (br s, 1H), 7.88 (t, J= 7.7 Hz, 1H), 7.76–7.74 (m, 3H), 7.56–7.51 (m, 2H), 7.42 (d, J= 3.4 Hz, 1H), 7.09–7.07 (m, 1H), 5.98 (d, J= 15.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 161.3,

150.9, 147.5, 140.0, 137.3, 134.9, 133.5, 132.4, 132.1, 131.5, 130.1, 130.0, 129.9, 128.9, 128.6, 127.1, 126.53, 126.48, 120.6, 118.3. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{15}N_2O_3S$, 375.0798; found, 375.0815.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(5-chlorothiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (53). The compound was synthesized according to the general procedure **C** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was filtered, was washed with water, followed by a diethyl ether wash to produce the title compound (78 mg, 54%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13–8.10 (m, 2H), 7.98–7.94 (m, 2H), 7.87 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.12 (d, J = 3.8 Hz, 1H), 5.89 (d, J = 15.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 161.2, 150.7, 147.4, 139.1, 136.7, 134.8, 131.8, 131.3 (3C), 130.4, 129.9, 129.7, 129.5, 128.5, 127.1, 126.6, 126.5, 120.6, 119.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{14}ClN_2O_3S$, 409.0408; found, 409.0424.

(*E*)-2-(2-(5-Bromothiophen-2-yl)vinyl)-3-(3-carboxyphenyl)quinazolin-4(3*H*)-one (54). The compound was synthesized according to the general procedure **D** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was filtered, was washed with water, followed by a diethyl ether wash to produce the title compound (82 mg, 61%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (br s, 1H), 8.15–8.11 (m, 2H), 8.01–7.96 (m, 2H), 7.88 (t, J = 7.1 Hz, 1H), 7.82–7.65 (m, 3H), 7.53 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 3.3 Hz, 1H) , 7.22 (d, J = 3.6 Hz, 1H), 5.90 (d, J = 15.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 161.2, 150.6, 147.4, 141.7, 137.1, 134.9, 133.4, 132.4, 132.1, 132.0, 131.1, 130.1 (2C), 129.9, 127.1, 126.7, 126.5, 120.6, 119.1, 114.2. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{14}BrN_2O_3S$, 452.9903; found, 452.9919.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(5-cyanophen-2-yl)vinyl)quinazolin-4(3*H*)-one (55). The compound was synthesized according to the general procedure **D** from compound **11**, while using pyridine, instead of acetic acid, as solvent. The mixture was concentrated *in vacuo* to give a yellow oil, which was triturated with diethyl ether (15 mL) to result in a precipitation. The precipitate was filtered and washed with diethyl ether, hexanes and a mixture of hexanes and EtOAc (50:50) giving the title compound (157 mg, 55%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (br s, 1H), 8.15–8.04 (m, 4H), 7.91–7.74 (m, 5H), 7.56–7.55 (m, 2H), 6.21 (d, J = 14.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 161.2, 150.2, 147.2, 146.7, 140.0, 137.0, 134.9, 133.5, 132.4, 130.6, 130.2, 130.1, 130.0 (2C), 127.2, 127.1, 126.5, 122.7, 120.8, 113.9, 108.7. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{14}N_3O_3S$, 400.0750; found, 400.0736.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(4-chlorothiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (56). The compound was synthesized according to the general procedure **D** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was filtered, was washed with water, followed by diethyl ether giving the title compound (212 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (br s, 1H), 8.14–8.12 (m, 2H), 8.02–7.96 (m, 2H), 7.89 (t, J = 7.64 Hz, 1H), 7.77–7.74 (m, 3H), 7.56–7.53 (m, 2H), 7.46 (s, 1H), 6.05 (d, J = 15.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 161.2, 150.5, 147.3, 140.5, 137.1, 134.9, 133.5, 132.4, 130.9, 130.0 (3C), 129.9, 127.2, 126.8, 126.5, 124.7,

123.2, 120.7, 119.7. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{14}ClN_2O_3S$, 409.0408; found, 409.0401.

(*E*)-3-(3-Carboxyphenyl)-2-(4-chlorostyryl)quinazolin-4(3*H*)-one (58). The compound was synthesized according to the general procedure **C** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was filtered, was washed with water, followed by ethanol and by hexanes giving the title compound (244 mg, 65%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (br s, 1H), 8.18–8.16 (m, 2H), 8.07 (d, J = 0.8 Hz, 1H), 7.95-7.91 (m, 2H), 7.89–7.77 (m, 3H), 7.58 (m, 1H), 7.47–7.43 (m, 4H), 6.36 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 161.3, 151.1, 147.4, 137.6, 137.2, 134.9, 134.3, 133.7, 133.5, 132.4, 130.1, 130.0, 129.3, 129.1, 127.3, 126.8, 126.5, 120.68, 120.65. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{16}ClN_2O_3$, 403.0844; found, 403.0829.

(*E*)-3-(3-Carboxyphenyl)-2-(4-iodostyryl)quinazolin-4(3*H*)-one (59). The compound was synthesized according to the general procedure **C** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, was washed with ethanol (10 mL, 3×) to produce the title compound (960 mg, 66%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 8.17–8.10 (m, 2H), 8.04–7.99 (m, 1H), 7.89 (ddd, J = 1.5, 7.2, 8.1 Hz, 1H), 7.83 (d, J = 15.5 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.75–7.73 (m, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.55 (5-line multiplet, ω= 15.0 Hz, assigned as a ddd, J = 8, 7, 1.1 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.34 (d, J = 15.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 161.8, 151.5, 147.8, 138.5, 138.3, 137.6, 135.3, 134.8, 133.9, 132.8, 130.5, 130.4, 130.0, 127.7, 127.2, 127.0, 121.1, 97.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{16}IN_2O_3$, 495.0200; found, 495.0179.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(pyridin-4-yl)vinyl)quinazolin-4(3*H*)-one (60). The compound was synthesized according to the general procedure **C** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water (20 mL, 3×), followed by ethanol (10 mL, 2×). The mixture was purified by column chromatography (DCM/methanol = 95:5) giving the title compound (0.97 g, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (m, 2H), 8.20 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 8.12 (m, 1H), 7.95 (m, 2H), 7.87–7.83 (m, 2H), 7.68–7.58 (m, 3H), 7.36 (m, 2H), 6.60 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.5, 162.2 (2C), 151.6, 151.4 (2C), 148.1, 142.7, 137.9, 137.2, 135.9, 134.2, 133.7, 131.1, 130.9 (2C), 128.3, 128.1, 127.4, 125.4, 122.5, 121.8. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_3$, 370.1186; found, 370.1168.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(fluoropyridin-4-yl)vinyl)quinazolin-4(3*H*)-one (61). To a pressure vessel were added compound **11** (300 mg, 1.07 mmol), 2-fluoroisonicotinaldehyde (1.34 g, 10.70 mmol) and anhydrous $ZnCl_2$ (14.6 mg, 0.11mmol). The vessel was sealed. The mixture was heated at 130 °C for 3 h. Methanol was added to the mixture and a precipitate was formed. The brown precipitate was filtered and washed with methanol (10 mL, 3×) to give crude product yellow powder. The yellow powder was triturated with hot methanol and hot diethyl ether to give the title compound (170 mg, 41%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s,1H), 8.23–8.10 (m, 3H), 8.04 (br s,1H), 7.96–7.89 (m, 1H), 7.88–7.79 (m, 2H), 7.76–7.70 (d, J = 4.9 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.36–7.27 (m, 2H), 6.71–6.61 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.5, 164.3 (d, J_{CF} = 234.9 Hz, 1C),

161.7, 151.0, 148.8 (d, J_{CF} = 15.6 Hz, 1C), 148.5 (d, J_{CF} = 8.7 Hz, 1C), 147.6, 137.2, 135.4, 135.3 (d, J_{CF} = 3.5 Hz, 1C), 133.4, 130.6, 130.4, 130.3, 127.9, 127.7, 127.0, 126.5, 121.4, 119.9 (d, J_{CF} = 3.8 Hz, 1C), 108.5, 108.1. ^{19}F NMR (376 MHz, DMSO-d_6) -68.56 (s, 1F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{15}FN_3O_3$, 388.1092; found, 388.1087.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(1-oxidopyridin-4-yl)vinyl)quinazolin-4(3*H*)-one (62). Compound **60** was dissolved in chloroform and *m*-CPBA was added. The reaction was stirred at rt for 6 h. The chloroform solution was washed with aqueous $NaHCO_3$ solution, 10% aqueous HCl solution, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude obtained was purified by column chromatography giving the title compound (104 mg, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.43 (d, *J* = 15.5 Hz, 1H), 7.47 (d, *J* = 7.10 Hz, 1H), 7.58–7.62 (m, 1H), 7.69–7.75 (m, 2H), 7.82 (m, 2H), 7.88–7.96 (m, 2H), 8.02–8.09 (m, 2H), 8.13–8.22 (m, 3H). ^{13}C NMR (101MHz, DMSO- d_6) δ 121.7, 123.3, 124.7, 125.7, 127.5, 128.3, 130.5, 130.9, 131.1, 132.3, 135.7, 135.9, 137.9, 139.5, 139.7, 140.0, 144.1, 146.2, 148.2, 151.8, 161.8, 162.3. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_4$, 386.1135; found, 386.1136.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(pyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (63). The compound was synthesized according to the general procedure **C** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water followed by diethyl ether giving the title compound (109 mg, 83%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.45 (d, *J* = 15.6 Hz, 1H), 7.35–7.38 (m, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.73–7.81 (m, 4H), 7.88–7.92 (m, 2H), 8.03 (s, 1H), 8.14–8.16 (m, 2H), 8.50 (d, *J* = 3.5 Hz, 1H), 8.65 (s, 1H), 13.27 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 120.7, 121.9, 124.0, 126.5, 126.9, 127.3, 130.0 (3C), 130.6, 132.4, 133.4, 133.8, 134.9, 135.6, 137.1, 147.3, 149.3, 150.4, 150.9, 161.3, 166.5. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_3$, 370.1186; found, 370.1175.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(6-cyanopyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (64). The compound was synthesized according to the general procedure **C** from compound **11**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water giving the title compound (106 mg, 76%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.63 (d, *J* = 15.0 Hz, 1H), 7.58 (s, 1H), 7.72–7.81 (m, 3H), 7.91–7.96 (m, 3H), 8.04–8.13 (m, 4H), 8.84 (s, 1H), 13.28 (br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 117.5, 120.8, 125.3, 126.6, 127.2, 127.4, 129.1, 130.1 (2C), 130.2, 132.2, 132.4, 133.5, 133.8, 134.2, 135.0, 135.3, 136.9, 147.2, 150.6, 150.7, 161.2, 166.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{15}N_4O_3$, 395.1139; found, 395.1156.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(2-fluoropyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (65). To a pressure vessel were Compound **11** (300 mg, 1.07 mmol), 2-fluoronicotinaldehyde (1.34 g, 10.70 mmol) and anhydrous $ZnCl_2$ (14.6 mg, 0.11mmol) added. The vessel was sealed and the mixture was heated at 130 °C for 3 h. The mixture was triturated in methanol/DCM mixture (10:90, 5 mL)for 10 mins to generate a yellow precipitate. The precipitate was filtered and washed with EtOAc to give the title compound (147 mg, 35%) as a fluffy yellow solid.[1] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s,1H), 8.24–8.10 (m, 3H), 8.10–8.00 (m, 2H), 7.95–7.79 (m, 3H), 7.6 (br s, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.35 (br s, 1H) 6.54 (d, *J* = 15.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 161.7, 160.7 (d, J_{CF} = 241.1 Hz, 1C), 151.1, 148.3 (d, J_{CF} = 15.5 Hz, 1C), 147.6, 141.0 (d, J_{CF} = 3.3 Hz, 1C), 137.6, 135.4, 133.9, 132.8, 130.7 (d, J_{CF} = 3.7 Hz, 1C), 130.5, 130.4, 127.9, 127.5, 126.9, 125.1 (d, J_{CF} = 8.0 Hz, 1C), 123.2 (d, J_{CF} =

4.0 Hz, 1C), 121.2, 118.2, 118.0. ^{19}F NMR (376 MHz, DMSO-d_6) -69.62 (s, 1F). HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{22}H_{15}FN_3O_3$, 388.1092; found, 388.1083.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(2-oxo-1,2-dihydropyridin-4-yl)vinyl)quinazolin-4(3*H*)-one (66). The compound was synthesized according to the general procedure **C** from compound **11** and 2-fluoroisonicotinaldehyde. Water (10 mL) was added to quench the reaction. The expected product was fully hydrolyzed when the reaction was quenched by water, which gave the title compound. A precipitate was formed after addition of water. The precipitate was filtered to give the title compound (279 mg, 67%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 11.59 (s, 1H), 8.19–8.09 (m, 2H), 8.04 (s, 1H), 7.90 (t, J = 7.4 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 4.6 Hz, 2H), 7.53–7.68 (m, 2H), 7.27 (d, J = 6.8 Hz, 1H), 6.44 (s,1H), 6.36 (d, J = 15.5 Hz, 1H), 5.95 (d, J = 6.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 101.8, 120.6, 121.3, 125.4, 127.0, 127.7, 127.9, 130.4, 130.5, 130.6, 132.8, 133.9, 135.4, 136.2, 136.8, 137.5, 146.8, 147.6, 150.9, 161.7, 163.1, 167.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_4$, 386.1135; found, 386.1135.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(6-oxo-1,6-dihydropyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (67). The compound was synthesized according to the general procedure **C** from compound **11** and 6-fluoronicotinaldehyde. Water (10 mL) was added to quench the reaction. The expected product was fully hydrolyzed when the reaction was quenched by water, which gave the title compound. A precipitate was formed. The precipitate was filtered to give crude product as a yellow powder. The crude product was further triturated with hot ethanol (2 mL, 2×) to give a precipitate. The precipitate was filtered to give the title compound (26 mg, 6%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 11.94 (s, 1H), 8.12 (t, J = 6.2 Hz, 2H), 7.97 (s, 1H), 7.93–7.64 (m, 6H), 7.51 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 9.3 Hz, 1H), 6.29 (d, J = 9.6 Hz, 1H), 5.95 (d, J = 15.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 114.5, 116.2, 121.0, 121.5, 126.9, 127.1, 127.6, 130.6, 130.66, 130.72, 133.0, 134.1, 135.5, 136.3, 137.5, 138.0, 139.4, 148.2, 152.3, 162.1, 162.6, 167.2 HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_4$, 386.1135; found, 386.1127.

(*E*)-3-(3-Carboxyphenyl)-2-(2-(2-oxo-1,2-dihydropyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (68). The compound was synthesized according to the general procedure **C** from compound **11** and 2-fluoronicotinaldehyde. Water (10 mL) was added to quench the reaction. The expected product was fully hydrolyzed when the reaction was quenched by water, which gave the title compound. Precipitate was formed. The precipitate was filtered to give the title compound (149 mg, 36%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H), 11.81 (s, 1H), 8.15–8.06 (m, 2H), 7.98–7.93 (m, 1H), 7.91–7.83 (m, 1H), 7.81–7.66 (m, 5H), 7.55–7.48 (m, 1H), 7.43 (dd, J = 1.6, 6.2 Hz, 1H), 7.29 (d, J = 15.1 Hz, 1H), 6.27 (t, J = 6.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 106.0, 120.9, 121.7, 125.1, 126.8, 126.9, 127.6, 130.3, 130.5, 132.7, 133.9, 135.2, 136.6, 136.9, 138.1, 143.5, 148.0, 152.8, 161.3, 161.9, 167.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_4$, 386.1135; found, 386.1127.

(*E*)-3-(3-Carboxy-2-fluorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (69). The compound was synthesized according to the general procedure **C** from compound **12**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and diethyl ether giving the title compound (68 mg, 49%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (d, J = 15.1 Hz, 1H), 7.51–7.61 (m, 2H), 7.71–7.73 (m, 2H), 7.81–7.84 (m, 4H), 7.95–7.99 (m, 2H), 8.09–8.18 (m, 2H), 13.58

(br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 111.7, 118.6, 120.2, 122.5, 125.0, 125.1, 125.3, 126.6, 127.5 (d, J_{CF} = 3.7 Hz, 1C), 128.6, 132.8, 133.5, 135.15, 135.17, 135.4, 138.1, 139.1, 147.2, 150.8, 154.1 (d, J_{CF} = 271.8 Hz, 1C), 160.6, 164.4 (d, J_{CF} = 2.9 Hz, 1C). ^{19}F NMR (376 MHz, DMSO-d_6) -119.7 (s, 1F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{15}FN_3O_3$, 412.1092; found, 412.1092.

(*E*)-3-(3-Carboxy-2,6-difluorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (70). The compound was synthesized according to the general procedure **C** from compound **13**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and diethyl ether giving the title compound (48 mg, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 (d, J= 14.9 Hz, 1H), 7.44–7.50 (m, 1H), 7.58–7.63 (m, 1H), 7.78–7.85 (m, 6H), 7.95–8.00 (m, 2H), 8.14–8.18 (m, 1H), 14.21 (br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 111.7, 113.3 (d, J_{CF} = 24.3 Hz, 1C), 118.6, 120.0, 120.8 (dd, J_{CF} = 13.3 Hz, 4.0 Hz, 1C), 122.4, 126.6, 127.4, 127.5, 128.7, 132.7, 133.7 (d, J_{CF} = 10.3 Hz, 1C), 135.4, 138.2, 139.1, 147.0, 150.7, 155.1 (d, J_{CF} = 247.1 Hz, 1C), 159.7 (d, J_{CF} = 251.7 Hz, 1C), 160.5, 161.3. ^{19}F NMR (376 MHz, DMSO-d_6) -118.1 (s, 1F), -108.6 (s, 1F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{14}F_2N_3O_3$, 430.0998; found, 430.1012.

(*E*)-3-(3-Carboxy-4-fluorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (71). The compound was synthesized according to the general procedure **C** from compound **14**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and diethyl ether giving the title compound (77 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.56 (d, J= 15.3 Hz, 1H), 7.56–8.14 (m, 12H), 13.54 (br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 118.4, 118.7, 120.5 (d, J_{CF} = 11.5 Hz, 1C), 120.7, 123.4, 126.5, 127.0, 127.4, 127.6, 128.1, 128.5, 132.7, 132.8, 134.9, 135.4 (d, J_{CF} = 8.8 Hz, 1C), 137.2, 139.3, 147.2, 150.8, 161.1 (d, J_{CF} = 259.5 Hz, 1C), 161.4, 164.3 (d, J_{CF} = 3.5 Hz, 1C). ^{19}F NMR (376 MHz, DMSO-d_6) -109.6 (s, 1F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{15}FN_3O_3$, 412.1092; found, 412.1088.

(*E*)-3-(5-Carboxy-3-fluorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (72). The compound was synthesized according to the general procedure **C** from compound **15**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and diethyl ether giving the title compound (87 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.57 (d, J= 15.6 Hz, 1H), 7.58 (ddd, J= 8.1 Hz, 7.0 Hz, 1.0 Hz, 1H), 7.68–7.71 (m, 2H), 7.79–7.82 (m, 4H), 7.87–7.96 (m, 4H), 8.15 (dd, J= 8.0 Hz, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 111.6, 117.0 (d, J_{CF} = 22.7 Hz, 1C), 118.2, 120.7, 121.2 (d, J_{CF} = 24.2 Hz, 1C), 123.2, 126.5, 127.1, 127.4, 128.5, 132.8, 134.2 (d, J_{CF} = 8.3 Hz, 1C), 135.5, 137.3, 138.5 (d, J_{CF} = 11.0 Hz, 1C), 139.2, 147.2, 150.6, 161.2, 162.1 (d, J_{CF} = 247.2 Hz, 1C), 165.5 (d, J_{CF} = 2.7 Hz, 1C). ^{19}F NMR (376 MHz, DMSO-d_6) -110.5 (s, 1F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{15}FN_3O_3$, 412.1092; found, 412.1080.

(*E*)-3-(5-Carboxy-2-chlorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (74). The compound was synthesized according to the general procedure **C** from compound **17**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was filtered, was washed with water and diethyl ether giving the title compound (9 mg, 17%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.46 (s, 1H), 8.28 (s, 1H), 8.16 (t, J= 7.48 Hz, 2H), 8.05–7.88 (m, 3H), 7.87–7.70 (m, 3H), 7.74–7.65 (m, 2H), 7.60 (t, J= 7.52 Hz, 1H), 6.50 (d, J= 15.49 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 161.1, 150.8, 147.7, 139.5, 138.7,

137.0, 135.8, 134.8, 133.3, 132.6, 132.5, 132.0, 131.2, 129.0, 128.0, 127.8, 127.1, 122.5, 120.9, 119.1, 112.2. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{14}ClN_3O_3$, 428.0796; found, 428.0805.

(*E*)-3-(3-Carboxy-6-methylphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (75). The compound was synthesized according to the general procedure **C** from compound **18**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was filtered, triturated with methanol giving the title compound (189 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 13.16 (s, 1H), 8.30–7.44 (m, 12H), 6.78–6.08 (m, 1H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 166.7, 161.2, 151.2, 147.9, 141.6, 139.7, 138.2, 136.6, 135.0, 132.9, 131.6, 130.9, 130.6, 130.5, 128.7, 127.8, 127.2, 126.7, 123.0, 121.2, 118.6, 112.2, 17.2. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{18}N_3O_3$, 428.1343; found, 428.1340.

(*E*)-3-(3-Carboxy-6-trifluoromethylphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (76). The compound was synthesized according to the general procedure **C** from compound **19**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was purified by silica gel column chromatography (DCM:acetic acid = 99:1) giving the desired compound (147 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.44 (d, J = 15.5 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.64–6.74 (m, 2H), 6.75–6.88 (m, 3H), 7.89–8.07 (m, 2H), 8.16 (t, J = 7.4 Hz, 2H), 8.27–8.46 (m, 2H), 13.76 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 112.2, 119.1, 120.8, 122.9, 123.0 (q, J_{CF} = 251.79 Hz, 1C), 127.0, 127.8, 128.0, 128.9, 129.1, 130.5, 130.8, 131.7, 133.3, 135.3, 135.8, 137.1, 138.4, 139.5, 147.5, 151.0, 161.9, 166.0. ^{19}F NMR (376 MHz, DMSO-d_6) -60.38 (s, 3F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{15}F_3N_3O_3$, 462.1060; found, 462.1072.

(*E*)-3-(5-Carboxy-3-hydroxyphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (77). The compound was synthesized according to the general procedure **C** from compound **20**. The mixture was cooled to rt to give yellow precipitation. The precipitation was filtered and washed with water (3×) to give the title compound (87 mg, 31%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 10.32 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 8.00–7.75 (m, 5H), 7.70–7.38 (m, 5H), 7.11 (s, 1H), 6.55 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 111.6, 116.9, 118.7, 120.2, 120.5, 120.8, 123.4, 126.5, 127.0, 127.4, 128.3, 132.9, 133.2, 134.9, 136.9, 137.9, 139.3, 147.2, 150.7, 158.4, 161.1, 166.5. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{16}N_3O_4$, 410.1135; found, 410.1154.

(*E*)-3-(5-Carboxy-2-hydroxyphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (78). The compound was synthesized according to the general procedure **D** from compound **21**. The solution cooled down to give a precipitate. The precipitate was filtered, washed with water giving the title compound (50 mg, 36%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 10.97 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 8.05–7.94 (m, 3H), 7.91 (t, J = 7.7 Hz, 1H), 7.86–7.76 (m, 3H), 7.62 (d, J = 8.2 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 6.59 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 112.0, 117.1, 119.1, 121.3, 122.8, 123.3, 123.9, 127.0, 127.4, 127.8, 128.7, 132.5, 132.9, 133.4, 135.4, 137.8, 139.8, 147.7, 151.7, 157.8, 161.4, 167.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{16}N_3O_4$, 410.1135; found, 410.1133.

(*E*)-3-(5-Carboxy-2-methoxyphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (79). The compound was synthesized according to the general procedure **C** from compound **22**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was

isolated by filtration, washed with water and, then, purified with silica gel column chromatography (EtOAc:hexanes:acetic acid = 30:70:1) giving the desired compound (6 mg, 5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.73 (s, 3H), 6.49 (d, J = 15.6 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.54–7.58 (m, 3H), 7.77–7.83 (m, 4H), 7.87–7.96 (m, 2H), 8.04 (d, J = 7.0 Hz, 1H), 8.14 (dd, J = 8.0 Hz, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 56.5, 112.0, 119.1, 119.28, 119.30, 119.4, 121.2, 123.3, 123.9, 127.02, 127.04, 127.5, 127.8, 128.5, 130.6, 133.4, 135.4, 137.6, 139.8, 147.7, 151.9, 161.2, 163.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{18}N_3O_4$, 424.1292; found: 424.1312.

(*E*)-2-(4-Cyanostyryl)-3-(3-methoxycarbonyl-2-hydroxyphenyl)quinazolin-4(3*H*)-one (80). The compound was synthesized according to the general procedure **C** from compound **23**. The solution was dried *in vacuo* to give yellow oil, which was further purified by silica gel column chromatography (EtOAc:hexanes = 40:60). The portions containing product were collected and concentrated *in vacuo* to give a light-yellow oil, which was further triturated with methanol and filtered to give the title compound (414 mg, 82%) as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.15 (dd, J = 1.2, 8.0 Hz, 1H), 7.96 (d, J = 15.6 Hz, 1H), 7.91 (ddd, J = 1.5, 7.2, 8.2 Hz, 1H), 7.84–7.77 (m, 3H), 7.67–7.55 (m, 5H), 7.53 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 15.6 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 53.1, 112.3, 117.9, 119.3, 121.1, 121.4, 123.4, 127.2, 127.7, 128.0, 128.6, 129.0, 131.4, 132.4, 133.6, 135.7, 138.2, 139.9, 147.9, 151.6, 154.1, 161.4, 166.4. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{18}N_3O_4$, 424.1292; found, 424.1284.

(*E*)-3-(3-Carboxy-2-hydroxyphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (81). To a 10 mL flask was compound **80** (100 mg, 0.24 mmol) dissolved in a mixture of DCM and methanol (9:1, 5 mL). A few drops of 1M NaOH (0.25 mL) was added dropwise with resulting mixture stirring for 30 mins. Remaining organic solvents were removed *in vacuo*. The resulting residue was taken up in 5 mL water before being acidified by 1N HCl (aq.), which resulted in precipitation. The precipitate was filtered, washed with water and dried *in vacuo* to give the title compound (30 mg, 31%) as a white solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.19 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 15.5 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.85–7.69 (m, 5H), 7.65 (d, J = 7.8 Hz, 2H), 7.60–7.45 (m, 2H), 6.76 (d, J = 15.5 Hz, 1H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 112.4, 118.2, 121.3, 121.4, 121.5, 123.1, 126.72, 126.68, 127.5, 128.0, 128.3, 129.9, 130.4, 132.7, 134.6, 137.6, 139.8, 147.8, 151.3, 153.4, 161.0, 168.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{16}N_3O_4$, 410.1135; found, 410.1147.

(*E*)-2-(4-Cyanostyryl)-3-(6-(methoxycarbonyl)pyridin-2-yl)quinazolin-4(3*H*)-one (82). The compound was synthesized according to the general procedure **C** from compound **24**. The mixture was cooled to rt and stirred for 12 h to give yellow precipitation. The precipitation was filtered and washed with acetic acid (3×) and water (3×) to give the title compound (0.94 g, 90%) as a yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (t, J = 7.7 Hz, 1H), 8.29 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.02–7.97 (m, 2H), 7.95–7.90 (m, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 6.38 (d, J = 15.5 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.4, 112.4, 119.3, 121.2, 123.3, 126.7, 127.1, 128.1, 128.2, 129.2, 129.3, 133.4, 136.0, 138.4, 139.8, 141.8, 147.9, 148.4, 150.6, 150.7, 161.9, 165.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{17}N_4O_3$, 409.1295; found, 409.1300.

(*E*)-2-(4-Cyanostyryl)-3-(6-carboxypyridin-2-yl)quinazolin-4(3*H*)-one (83). Compound **82** (260 mg, 0.64 mmol) was first dissolved in DCM/MeOH/H_2O (10/1/1). Extra MeOH was added if the solution is not clear. 1M NaOH (aq.) solution was then added dropwise at rt until the pH > 10 and resulting solution was continued for 30 min. After compound **82** was all reacted, 1N HCl (aq.) solution was added dropwise until pH = 8. The residue solvent was distilled off *in vacuo* until a precipitate was formed. The precipitate was left at rt for 12 h and was further filtered to give white solid, followed by trituration with hot water to give the title compound (64 mg, 26%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.40 (d, J = 15.5 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.3 Hz, 1H), 8.01–7.90 (m, 3H), 8.17 (d, J = 7.9 Hz, 1H), 8.37–8.24 (m, 2H), 13.52 (br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 112.3, 121.2, 123.4, 126.6, 127.1, 128.1, 128.2, 128.7, 129.2, 129.6, 133.5, 136.0, 138.3, 139.8, 141.6, 147.8, 149.5, 150.4, 150.8, 161.9, 165.9. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{15}N_4O_3$, 395.1139; found, 395.1127.

(*E*)-2-(4-Cyanostyryl)-3-(4-carboxypyridin-2-yl)quinazolin-4(3*H*)-one (84). The compound was synthesized according to the general procedure **C** from compound **26**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and, then, with diethyl ether giving the desired compound (54 mg, 25%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (dd, J = 0.7, 5.1 Hz, 1H), 8.20–8.14 (m, J = 1.9 Hz, 2H), 8.06 (dd, J = 1.5, 5.1 Hz, 1H), 8.00–7.90 (m, 2H), 7.86–7.76 (m, 3H), 7.69 (br d, J = 8.32 Hz, 2H), 7.64–7.57 (m, 1H), 6.47–6.38 (d, J = 15.53 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 112.1, 119.1, 121.0, 123.6, 124.6, 124.7, 127.0, 127.8, 128.0, 129.0, 133.2, 135.7, 137.7, 139.7, 141.9, 147.6, 150.7, 151.2, 151.4, 161.7, 165.9. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{16}N_3O_4$, 395.1139; found, 395.1144.

(*E*)-2-(4-Cyanostyryl)-3-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4(3*H*)-one (85). The compound was synthesized according to the general procedure **C** from compound **27**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and, then, with hexanes giving the desired compound (93 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.57 (d, J = 15.1 Hz, 1H), 6.96–7.07 (m, 3H), 7.56–7.60 (m, 3H), 7.78–7.92 (m, 5H), 8.13 (d, J = 6.6 Hz, 1H), 10.90 (d, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 108.8, 109.2, 118.6, 120.9, 121.0, 123.7, 126.5, 126.8, 127.3, 128.2, 129.4, 130.2, 130.3, 132.9, 134.7, 136.5, 139.4, 147.2, 151.5, 155.5, 161.5. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{16}N_5O_2$, 406.1299; found, 406.1279.

(*E*)-2-(4-Cyanostyryl)-3-(2-thioxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4(3*H*)-one (86). The compound was synthesized according to the general procedure **C** from compound **28**. Water was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water giving the desired compound (94 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.53 (d, J = 15.6 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.27–7.31 (m, 2H), 7.54–7.61 (m, 3H), 7.77–7.80 (m, 3H), 7.87–7.93 (m, 2H), 8.14 (d, J = 7.8 Hz, 1H), 12.81 (br s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 109.9, 110.3, 111.5, 118.7, 120.9, 123.0, 126.5 (2C), 126.9, 127.3, 128.3, 131.1, 132.7, 132.9 (2C), 134.8, 136.7, 139.3, 147.2, 151.3, 161.5, 169.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{16}N_5OS$, 422.1070; found, 422.1073.

(*E*)-3-(1*H*-Benzo[*d*]imidazol-6-yl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (87). The compound was synthesized according to the general procedure **C** from compound **29**. Water

was poured into the concentrated mixture, which resulted in a precipitate. The solid was isolated by filtration, washed with water and, then, with a mixture of water and ethanol. The solid was further purified by crystallization in hot ethanol giving the desired compound (47 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.53 (d, J = 14.5 Hz, 1H), 7.24 (s, 1H), 7.50–7.90 (m, 10 H), 8.15 (s, 1H), 8.39 (s, 1H), 12.77 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 111.4, 112.5, 118.6, 119.7, 120.7, 120.9, 122.1, 123.7, 126.3, 126.6, 126.7, 126.9, 127.3, 128.1, 132.9, 134.8, 136.5, 139.4, 143.9, 147.3, 151.5, 161.6. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{24}H_{16}N_5O$, 390.1349; found, 390.1342.

(*E*)-2-(4-Cyanostyryl)-3-(3-(2,2,2-trifluoroacetamido)phenyl)quinazolin-4(3*H*)-one (88). Compound **111** (100 mg, 0.51 mmol) was dissolved in trifluoroacetic acid (2 mL). A portion of trifluoroacetic anhydride (1 mL, 7.20 mmol) added. The reaction was stirred for 8 h. The solution was concentrated *in vacuo* to give a yellow oil. The oil was triturated with DCM (2×) and diethyl ether (2×) to give the title compound (109 mg, 97%) as light-yellow crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 8.00–7.75 (m, 7H), 7.72–7.51 (m, 4H), 7.36 (d, J = 7.6 Hz, 1H), 6.54 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 155.2 (q, J_{CF} = 37.1 Hz, 1C), 151.1, 147.6, 139.8, 137.9, 137.6, 137.5, 135.4, 133.3, 130.8, 128.7, 127.8, 127.6, 127.0, 126.7, 123.8, 122.4, 122.0, 121.2, 119.1, 116.2 (q, J_{CF} = 289.3 Hz, 1C), 112.1. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{25}H_{16}F_3N_4O_2$, 461.1220; found, 461.1230.

(*E*)-3-(3-(3-(*N*-Boc-methylamino)propanamido)phenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (89a). 3-(*N*-((*tert*-Butoxy)carbonyl)-*N*-methylamino)propanoic acid (30 mg, 0.15 mmol), EDC·HCl (115 mg, 0.6 mmol) and HOBt·H_2O (81 mg, 0.6 mmol) were dissolved in anhydrous pyridine (4 mL) and the mixture was stirred for 2 h at rt under nitrogen atmosphere. Then, a solution of compound **111** (66 mg, 0.18 mmol) in anhydrous pyridine (4 mL) was added to the reaction. The system was stirred at rt for 12 h under nitrogen atmosphere. The reaction mixture was quenched with $NaHCO_3$ saturated solution (15 mL). The resulting mixture was washed with EtOAc (15 mL, 3×). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure until dryness to give the crude product (40 mg, 49%) without further purification. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{32}H_{32}N_5O_4$, 550.2449; found, 550.2457.

(*E*)-2-(4-Cyanostyryl)-3-(3-(3-(methylamino)propanamido)phenyl)quinazolin-4(3*H*)-one (89). Compound **89a** (40 mg, 0.07 mmol) was dissolved in anhydrous DCM (3 mL) and trifluoroacetic acid (2 mL) and the reaction was stirred at rt for 24 h. The mixture was quenched with $NaHCO_3$ saturated solution (10 mL). The resulting mixture was washed with EtOAc (10 mL, 3×) The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure until dryness giving the desired compound (25 mg, 80%). ^{1}H NMR (400 MHz, acetone-d_6) δ 2.09 (s, 3H), 3.03 (t, J = 6.4 Hz, 2H), 3.43 (t, J = 6.7 Hz, 2H), 6.71 (d, J = 15.5 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.72–7.81 (m, 4H), 7.87 (td, J = 7.80 Hz, 1.5 Hz, 1H), 7.93 (br s, 1H), 8.01 (d, J = 15.5 Hz, 1H), 9.74 (br s, 1H), 10.47 (br s, 1H). ^{13}C NMR (101 MHz, acetone-d_6) δ 33.5, 33.6, 46.1, 113.4, 119.2, 120.8, 120.9, 122.3, 124.6, 124.9, 127.66, 127.74, 128.6, 129.3, 130.9, 133.6, 135.5, 138.2, 138.5, 140.8, 141.4, 148.7, 152.0, 162.4, 170.1. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{27}H_{24}N_5O_2$, 450.1925; found, 450.1937.

(*E*)-2-(4-Cyanostyryl)-3-(3-(3-(1-trityl-1*H*-imidazol-5-yl)propanamido)phenyl)quinazolin-4(3*H*)-one (90a). Starting material 3-(1-trityl-*1H*-imidazol-5-yl)propanoic acid (41 mg, 0.11 mmol), HATU (47 mg, 0.12 mmol) were dissolved in anhydrous DMF (5 mL) and the mixture was stirred for 10 min at rt under nitrogen atmosphere. Then, compound **111** (60 mg, 0.16 mmol) was added to the reaction mixture, which was stirred for 20 min at rt. Then, diisoproprylethylamine (43 mg, 57 μL, 0.33 mmol) was added and the mixture was stirred at rt for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL). The resulting mixture was washed with EtOAc (10 mL, 3×). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure until dryness. The mixture was purified by preparative TLC using hexanes:EtOAc (1:1) as eluent giving the crude product (36 mg, 45%) without purification. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{48}H_{37}N_6O_2$, 729.2973; found, 729.2975.

(*E*)-2-(4-Cyanostyryl)-3-(3-(3-(1*H*-imidazol-5-yl)propanamido)phenyl)quinazolin-4(3*H*)-one (90). Compound **90a** (36 mg, 0.05 mmol) was dissolved in a mixture of trifluoroacetic acid (0.8 mL) and DCM (3 mL) and stirred at room temperature for 8 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL). The resulting mixture was washed with DCM (10 mL, 2×). The organic layers were combined, washed with NaCl saturated solution, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure until dryness. The mixture was washed with diethyl ether and the insoluble precipitate was isolated by filtration giving the desired compound (9 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.65 (t, J = 7.1 Hz, 2H), 2.81 (t, J = 6.3 Hz, 2H), 6.54 (d, J = 15.8 Hz, 1H), 6.81 (s, 1H), 7.12–7.30 (m, 3H), 7.50–7.53 (m, 1H), 7.54–7.60 (m, 3H), 7.71–7.74 (m, 2H), 7.78–7.83 (m, 2H), 7.88–7.96 (m, 2H), 8.15 (d, J = 7.8 Hz, 1H), 10.28 (s, 1H), 12.04 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 22.9, 36.8, 85.6, 112.3, 119.3, 119.8, 120.4, 121.5, 124.1, 127.2, 127.4, 127.8, 128.1, 128.2, 128.5, 128.9, 130.7, 133.6, 135.3, 135.6, 137.6, 140.1, 141.2, 147.9, 151.5, 161.8, 171.7. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{23}N_6O_2$, 487.1877; found, 487.1861.

(*E*)-2-(4-Cyanostyryl)-3-(3-(2-morpholinoacetamido)phenyl)quinazolin-4(3*H*)-one (91). 4-Morpholineacetic acid (22 mg, 0.15 mmol), EDC·HCl (115 mg, 0.6 mmol) and HOBt·H_2O (81 mg, 0.6 mmol) were dissolved in anhydrous pyridine (4 mL) and the mixture was stirred for 2 hours at rt under nitrogen atmosphere. Then, compound **111** (66 mg, 0.18 mmol) was dissolved in anhydrous pyridine (4 mL) and added to the reaction. The system was stirred at rt for 12 h under nitrogen atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL). The resulting mixture was washed with EtOAc (10 mL, 3×). The organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure until dryness. The mixture was purified by preparative TLCs twice (hexanes:EtOAc:triethylamine = 75:25:0.5, 1×; 100% EtOAc, 1×) giving the desired compound (41 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (br s, 4H), 3.22 (br s, 2H), 3.79 (br s, 4H), 6.54 (d, J = 15.5 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.47–7.62 (m, 4H), 7.65 (s, 1H), 7.75–7.88 (m, 3H), 7.97 (d, J = 15.5 Hz, 1H), 8.30 (d, J = 7.70 Hz, 1H), 9.42 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.7, 62.1, 66.7, 112.6, 118.4, 119.6, 120.5, 120.9, 123.1, 124.2, 127.1, 127.2, 127.6, 128.1, 130.6, 132.5, 134.8, 137.3, 137.6, 139.1, 139.5, 147.4, 150.5, 162.1, 167.8. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{25}N_5O_3$, 492.2030; found, 492.2049.

(*E*)-2-(4-Cyanostyryl)-3-(3-(3-((1*H*-imidazol-5-yl)methyl)ureido)phenyl)quinazolin-4(3*H*)-one (92). Compound **111** (100 mg, 0.27 mmol) was dissolved in anhydrous pyridine (5 mL) at rt under nitrogen atmosphere. The solution was stirred at ice-bath temperature for 30 mins before addition of phenyl chloroformate (43 mg, 34 µL, 0.273 mmol). The mixture was stirred for 1 h. After monitoring the complete conversion of compound **111** by analytical TLC, a suspension of *1H*-imidazole-5-methanamine hydrochloride (97 mg, 0.54 mmol) in anhydrous DCM (1 mL) was added to the reaction mixture. The mixture was stirred for 1 h at 40 ºC until formation of a yellow precipitate. Heptanes (20 mL) were added to the mixture and the resulting suspension was refrigerated for 2 h. The precipitate was filtered and washed with a mixture of DMF and water (10 mL, 4:1) giving the title compound (18 mg, 14%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50 (overlapped), 6.54 (d, J = 15.5 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 7.48–7.63 (m, 7H), 7.77–7.81 (m, 3H), 7.86–7.93 (m, 2H), 8.14 (d, J = 7.9 Hz, 1H), 9.09 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 36.5, 111.6, 118.4, 118.5, 118.6, 118.9, 119.0, 120.8, 122.31, 122.34, 123.4, 126.5, 127.0, 127.3, 128.2, 130.0, 131.9, 134.9, 136.8, 137.1, 139.4, 140.7, 141.2, 150.8, 152.4, 161.1. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{28}H_{22}N_7O_2$, 488.1829; found, 488.1827.

(*E*)-2-(4-Cyanostyryl)-3-(3-(3-((1*H*-imidazol-5-yl)ethyl)ureido)phenyl)quinazolin-4(3*H*)-one (93). Compound **111** (100 mg, 0.27 mmol) was dissolved in anhydrous pyridine (5 mL) at rt under nitrogen atmosphere. The solution was stirred at ice-bath temperature for 30 mins before addition of phenyl chloroformate (43 mg, 34 µL, 0.273 mmol). The mixture was stirred for 1 h. After the complete conversion of compound **111**, a suspension of *1H*-imidazole-5-ethanamine (60 mg, 0.54 mmol) in anhydrous DCM (1 mL) was added to the reaction system. The mixture was stirred for 1 hour at 40 ºC until formation of a yellow precipitate. Heptanes (20 mL) were added to the mixture and the resulting suspension was refrigerated for 2 h. The precipitate was filtered and washed with heptanes (10 mL, 2×) to give the crude product. The crude was then crystallized in a solution of ethanol and water (1:1, 2 mL). The crystals were isolated, washed with diethyl ether giving the title compound (51 mg, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.64 (t, J = 6.7 Hz, 2H), 3.33 (overlapped), 6.29 (t, J = 5.5 Hz, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.82 (s, 1H), 6.97 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.50–7.60 (m, 6H), 7.65–7.95 (m, 6H), 8.15 (d, J = 8.5 Hz, 1H), 8.85 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 27.29, 27.33, 111.4, 117.3, 118.0, 118.5, 120.6, 121.0, 123.3, 126.4, 126.9, 127.2, 127.9, 128.0, 129.8, 132.8, 132.9, 134.6, 134.8, 136.7, 136.9, 139.3, 141.8, 147.1, 150.7, 154.8, 160.9. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{29}H_{24}N_7O_2$, 502.1986; found, 502.1983.

(*E*)-2-(4-Cyanostyryl)-3-(3-sulfamoylphenyl)quinazolin-4(3*H*)-one (94). The compound was synthesized according to the general procedure **D** from compound **31**. The mixture was cooled to rt to give a yellow precipitate. The precipitate was filtered and washed with water (3×) to give the title compound (127 mg, 67%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, J = 1.1, 7.9 Hz, 1H), 8.03 (td, J = 1.4, 7.8 Hz, 1H), 8.00–7.89 (m, 3H), 7.87–7.79 (m, 4H), 7.76 (ddd, J = 1.2, 1.9, 7.9 Hz, 1H), 7.64–7.54 (m, 5H), 6.46 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.7, 151.0, 147.6, 146.0, 139.7, 137.7, 137.6, 135.5, 133.3, 133.1, 131.1, 128.7, 127.9, 127.6, 127.1, 127.0, 126.8, 123.6, 121.2, 119.1, 112.1. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{23}H_{17}N_4O_3S$, 429.1016; found, 429.1032.

(*E*)-2-(4-Cyanostyryl)-3-(3-(*N*-acetylsulfamoyl)phenyl)quinazolin-4(3*H*)-one (95). Compound **94** (200 mg, 0.47 mmol) was pretreated with sodium hydride (56 mg, 3.40 mmol) for 15 mins in a 10-mL single-necked round-bottom flask . Acetic anhydride (238 mg, 3.4 mmol) was added to the flask dropwise. The mixture was stirred for 1.5 h before the reaction was quenched by addition of ice. A 1 N solution of HCl (aq.) was added to acidify the solution to pH = 4. The solution was then washed with EtOAc (10 mL, 3×). The combined organic fraction was washed with water (10 mL, 3×) and brine (10 mL, 3×), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a yellow solid, which was further triturated in the presence of a mixture of DCM and methanol (5 mL, 9:1) to give the title compound (61 mg, 28%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.22–8.05 (m, 3H), 7.99–7.75 (m, 7H), 7.63 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 15.5 Hz, 1H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.6, 161.7, 151.0, 147.7, 141.0, 139.7, 137.70, 137.68, 135.4, 135.0, 133.2, 131.3, 129.1, 128.8, 128.7, 127.9, 127.5, 127.0, 123.6, 121.2, 119.1, 112.1, 23.7. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{19}N_4O_4S$, 471.1122; found, 471.1124.

(*E*)-3-(3-Carbamoylphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (96). Compound **32** (550 mg, 1.96 mmol) and 4-formylbenzonitrile (310 mg, 2.36 mmol) were dissolved in acetic acid (10 mL) in a 10-mL round-bottom flask. The mixture was refluxed for 8 h. On cooling the mixture to rt, a yellow precipitate formed. The precipitate was filtered and washed with water (3×) to give the title compound (768 mg, 86%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, J = 1.1, 7.9 Hz, 1H), 8.12 (br s, 1H), 8.09 (td, J = 1.4, 7.6 Hz, 1H), 7.99–7.88 (m, 3H), 7.86–7.77 (m, 3H), 7.72 (t, J = 7.7 Hz, 1H), 7.67 (td, J = 1.6, 7.8 Hz, 1H), 7.63–7.52 (m, 4H), 6.50 (d, J = 15.6 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 161.7, 151.3, 147.6, 139.7, 137.5, 137.2, 136.2, 135.5, 133.3, 132.3, 130.2, 128.8, 128.7, 128.6, 127.8, 127.6, 127.0, 123.8, 121.1, 119.1, 112.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{17}N_4O_2$, 393.1346; found, 393.1343.

(*E*)-2-(4-Cyanostyryl)-3-(3-((1,3-dioxoisoindolin-2-yl)methyl)phenyl)quinazolin-4(3*H*)-one (97). The compound was synthesized according to the general procedure **C** from compound **33**. Saturated $NaHCO_3$ (10 mL) was added to the concentrated reaction mixture. The resulting mixture was washed with EtOAc (10 mL, 3×). The organic layers were collected, washed with saturated NaCl, dried over anhydrous Na_2SO_4 and the organic solvent was removed under reduced pressure until dryness. The mixture was purified by preparative TLC (DCM:EtOAc = 10:1) giving the title compound (27 mg, 19%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.85 (d, J = 14.7 Hz, 1H), 4.97 (d, J = 14.7 Hz, 1H), 6.40 (d, J = 15.8 Hz, 1H), 7.27–7.29 (m, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.40 (br s, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.49–7.53 (m, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.62–7.64 (m, 1H), 7.71–7.76 (m, 4H), 7.81–7.82 (m, 2H), 7.91 (d, J = 15.5 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 41.4, 112.8, 118.6, 121.0, 122.9, 123.6, 127.3, 127.4, 127.5, 128.3, 128.4, 129.1, 130.0, 130.6, 132.0, 132.6, 134.4, 135.1, 136.9, 138.3, 138.7, 139.5, 140.2, 151.2, 161.9, 167.9. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{32}H_{21}N_4O_3$, 509.1608; found, 509.1619.

(*E*)-3-(3-(Aminomethyl)phenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (98). Compound **97** (20 mg, 0.04 mmol) and lithium hydroxide (2 mg, 0.08 mmol) were dissolved in a mixture of water and THF (1:2, 3 mL) and stirred at rt for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL). The resulting mixture was washed with EtOAc (10

mL, 3×). The organic layers were collected, washed with saturated NaCl, dried over anhydrous Na_2SO_4 and the organic solvent was removed under reduced pressure until dryness. The crude extract was washed with diethyl ether and the precipitate was isolated by filtration giving the title compound (13 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 2H), 6.50 (d, J = 15.5 Hz, 1H), 7.31–7.49 (m, 3H), 7.55–7.63 (m, 4H), 7.78–7.81 (m, 3H), 7.90–7.94 (m, 2H), 8.15 (d, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 40.3, 111.6, 118.6, 120.7, 123.4, 126.5, 127.1, 127.4 ,127.5, 128.2, 128.5, 129.6, 132.80, 132.82, 132.9, 135.0, 136.7, 137.9, 139.4, 147.2, 150.9, 161.2. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{19}N_4O$, 379.1553; found, 379.1560.

(*E*)-2-(4-Cyanostyryl)-3-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)quinazolin-4(3*H*)-one (99). The compound was synthesized according to the general procedure **C** from compound **34**. The solvent was evaporated *in vacuo* to give a yellow oil. The oil was triturated in the presence of EtOAc to produce the title compound (26 mg, 20%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (br s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.94–7.90 (m, 2H), 7.81–7.78 (m, 3H), 7.63–7.55 (m, 4H), 7.48 (d, J = 7.4 Hz, 1H), 7.40 (br s, 2H), 6.46 (d, J = 15.5 Hz, 1H), 4.49 (d, J = 4.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.2, 156.5 (q, J = 37.3 Hz), 150.8, 147.2, 139.4, 136.91, 136.88, 134.9, 132.8, 129.9, 128.24, 128.20, 128.0, 127.9, 127.4, 127.1, 126.5, 123.3, 120.8, 118.6, 117.4, 116.0 (q, J = 288.3 Hz), 111.6, 42.3. ^{19}F NMR (376 MHz, DMSO-d_6) -74.33 (s, 3F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{18}F_3N_4O_2$, 475.1376; found, 475.1356.

(*E*)-2-(4-Cyanostyryl)-3-(2-hydroxyphenyl)quinazolin-4(3*H*)-one (100). The compound was synthesized according to the general procedure **C** from compound **35**. Water was added to the concentrated reaction mixture, which resulted in a precipitate. The precipitate was triturated in the presence of EtOAc to give the title compound (355 mg, 48%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.96–7.88 (m, 2H), 7.84–7.78 (m, 3H), 7.58–7.55 (m, 3H), 7.41 (t, J = 7.8 Hz 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.56 (d, J = 15.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 153.6, 151.9, 147.8, 139.9, 137.4, 135.3, 133.4, 131.3, 130.6, 128.5, 127.7, 127.4, 127.0, 124.1, 123.6, 121.4, 120.2, 119.1, 117.3, 112.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{16}N_3O_2$, 366.1237; found, 366.1248.

(*E*)-2-(4-Cyanostyryl)-3-(2-nitrophenyl)quinazolin-4(3*H*)-one (101). The compound was synthesized according to the general procedure **C** from compound **36**. The reaction mixture was concentrated to give yellow oil, which was purified by preparative TLC plate (EtOAc:hexanes = 50:50) to give the title compound (33 mg, 7%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 6.4 Hz, 1H), 8.27–7.44(m, 12H), 6.67 (d, J = 15.4 Hz, 1H).^{13}C NMR (101 MHz, DMSO-d_6) δ 112.2, 119.1, 120.5, 123.6, 126.6, 127.0, 127.9, 128.0, 129.1, 130.4, 131.8, 132.3, 133.2, 135.9, 136.0, 138.3, 139.6, 146.5, 147.7, 151.1, 161.2. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{15}N_4O_3$, 395.1139; found, 395.1122.

(*E*)-3-(2-Carboxyphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (102). The compound was synthesized according to the general procedure **C** from compound **37**. The reaction mixture was concentrated to give a white precipitate, which was filtered and washed with acetic acid (5 mL, 3×) to give the title compound (219 mg, 53%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.22–8.10 (m, 2H), 7.95–7.87 (m, 2H), 7.87–7.77 (m, 4H), 7.76–7.69 (m, 1H), 7.63–7.53 (m, 4H), 6.45 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz,

DMSO-d_6) δ 112.0, 119.1, 121.2, 123.7, 126.9, 127.4, 127.77, 127.81, 128.7, 130.4, 131.1, 132.2, 133.3, 134.2, 135.4, 137.0, 137.4, 139.7, 147.8, 151.5, 161.7, 166.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{16}N_3O_3$, 394.1186; found, 394.1182.

(*E*)-2-(4-Cyanostyryl)-3-(4-nitrophenyl)quinazolin-4(3*H*)-one (103). The compound was synthesized according to the general procedure **C** from compound **38**. The mixture was cooled to rt to give yellow precipitation. The precipitation was filtered and washed with acetic acid (3×) and EtOAc (3×) to give the title compound (0.53 g, 43%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50–8.47 (m, 1H), 8.47–8.44 (m, 1H), 8.16 (dd, J = 1.1, 7.9 Hz, 1H), 7.95 (d, J = 15.5 Hz, 1H), 7.96–7.89 (m, 1H), 7.86–7.78 (m, 5H), 7.72–7.66 (m, 2H), 7.62–7.56 (s, 1H), 6.51 (d, J = 15.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 112.1, 119.1, 121.1, 123.6, 125.4, 127.0, 127.6, 127.9, 129.1, 131.3, 133.2, 135.6, 138.0, 139.6, 143.1, 147.7, 148.3, 150.7, 161.5. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{15}N_4O_3$, 395.1139; found, 395.1134.

(*E*)-3-(4-Aminophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (104). To a precipitate of (**103**) (400 mg, 1.01 mmol) in EtOH was Tin(Ⅱ) chloride (577 mg, 3.04 mmol) added. A few drops of HCl (12 N) solution was added and the mixture was heated up to reflux for 5 h. The precipitate was filtered to recover 220 mg of **103** as a yellow solid. The pH was adjusted to 10 by the addition of NaOH (1 N) and the resulting precipitate was filtered again. The filtrate was concentrated *in vacuo* to give a yellow oil, which was taken up in EtOAc (10 mL) and washed with water (10 mL, 3×). The organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed and the yellow oil was connected to pump for several hours. The oil was purified by silica-gel column chromatography (EtOAc:hexanes = 1:1). The resulting yellow solid was triturated with EtOAc (3×) to give the title compound (125 mg, 47%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 7.9 Hz, 1H), 7.92–7.80 (m, 4H), 7.76 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.06–6.99 (m, 2H), 6.70 (br d, J = 8.6 Hz, 2H), 6.64 (d, J = 15.7 Hz, 1H), 5.50 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 111.9, 114.5, 119.1, 121.3, 124.4, 124.7, 127.0, 127.3, 127.7, 128.5, 129.6, 133.4, 135.1, 136.7, 140.0, 147.7, 149.8, 152.4, 162.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{17}N_4O$, 365.1397; found, 365.1398.

(*E*)-2-(4-Cyanostyryl)-3-(pyridin-3-yl)quinazolin-4(3*H*)-one (105). The compound was synthesized according to the general procedure **C** from compound **42**. The mixture was cooled to rt to produce a yellow precipitate. The precipitate was filtered and washed with water (3×) and EtOAc (3×), followed by recrystallization from methanol to give the title compound (24 mg, 23%) as yellow crystals. ^{1}H NMR (400 MHz, CD_3OD) 8.77 (dd, J = 1.5, 4.9 Hz, 1H), 8.66 (dd, J = 0.6, 2.4 Hz, 1H), 8.25 (ddd, J = 0.5, 1.5, 8.0 Hz, 1H), 7.98 (ddd, J = 1.5, 2.5, 8.1 Hz, 1H), 7.96 (d, J = 15.5 Hz, 1H), 7.94–7.88 (m, 1H), 7.85 (ddd, J = 0.5, 1.2, 8.2 Hz, 1H), 7.75–7.67 (m, J = 2.0 Hz, 3H), 7.61–7.54 (m, J = 2.7 Hz, 3H), 6.56 (d, J = 15.5 Hz, 1H). ^{1}H NMR (400 MHz, DMSO-d_6) 8.77 (dd, J = 1.4, 4.8 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.16 (dd, J = 1.2, 8.0 Hz, 1H), 8.00 (ddd, J = 1.6, 2.4, 8.1 Hz, 1H), 7.97–7.88 (m, 2H), 7.87–7.78 (m, 3H), 7.71–7.62 (m, 3H), 7.62–7.56 (m, 1H), 6.52 (d, J = 15.6 Hz, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.8, 151.3, 150.7, 150.2, 147.7, 139.7, 137.7, 137.5, 135.6, 134.0, 133.3, 128.8, 127.9, 127.7, 127.0, 125.0, 123.9, 121.0, 119.1,112.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{15}N_4O$, 351.1240; found, 351.1239.

(*E*)-2-(4-Cyanostyryl)-3-(1-oxidopyridin-3-yl)quinazolin-4(3*H*)-one (106). Compound **105** (220 mg, 0.64 mmol) was dissolved in 20 mL DMF in a 50-mL round-bottom flask. The solution was charged with *m*-CPBA (264 mg, 16 mmol), which was then stirred at rt for 12 h. A precipitate started forming after 6 h of stirring. The resulting yellow suspension was filtered and washed with DMF (3×) and water (3), followed by recrystallization from DMF to give the title compound (101 mg, 44%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) 8.58 (t, J = 1.5 Hz, 1H), 8.41 (ddd, J = 0.9, 1.8, 6.5 Hz, 1H), 8.16 (dd, J = 1.2, 8.0 Hz, 1H), 7.95 (d, J = 15.5 Hz, 1H), 7.96–7.88 (m, 1H), 7.86–7.77 (m, 5H), 7.67–7.56 (m, 2H), 7.53 (ddd, J = 0.9, 1.7, 8.2 Hz, 1H), 6.78 (d, J = 15.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.5, 151.0, 147.6, 140.23, 140.16, 139.7, 138.2, 136.5, 135.7, 133.2, 129.3, 127.9, 127.7, 127.2, 127.0, 126.8, 123.7, 121.0, 119.2, 112.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{15}N_4O_2$, 367.1190; found, 367.1203.

(*E*)-3-(3-Cyanophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (107). The compound was synthesized according to the general procedure **C** from compound **39**. The mixture was cooled to rt to give yellow precipitation. The precipitation was filtered and washed with water (3×), followed by recrystallization in EtOAc to give the title compound (166 mg, 21%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) 8.15 (dd, J = 1.1, 7.9 Hz, 1H), 8.11 (t, J = 1.5 Hz, 1H), 8.07 (td, J = 1.5, 7.5 Hz, 1H), 7.97–7.89 (m, 2H), 7.87 (ddd, J = 1.4, 2.0, 8.1 Hz, 1H), 7.85–7.78 (m, 4H), 7.68 (br d, J = 8.3 Hz, 2H), 7.62–7.55 (m, 1H), 6.52 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 151.1, 147.6, 139.7, 138.0, 137.8, 135.6, 134.8, 133.7, 133.6, 133.3, 131.5, 129.0, 127.9, 127.6, 127.0, 123.7, 121.1, 119.1, 118.6, 113.1, 112.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{15}N_4O$, 375.1240; found, 375.1250.

(*E*)-2-(4-Cyanostyryl)-3-(3-Azidophenyl)quinazolin-4(3*H*)-one (108). Compound **111** (200 mg, 0.55 mmol) was dissolved in acetic acid (10 mL) and water (10 mL) at ice-water temperature in a 50-mL round-bottom flask . Sodium nitrite (57 mg, 0.83 mmol, 1.5 eq,) in 5 mL water was added and the reaction was allowed to continue for 1 h, at which time the reaction had reached completion. Sodium azide (54 mg, 0.83 mmol, 1.5 eq) in 5 mL water was added and the reaction was continued for 1 h at rt. The reaction mixture was diluted with water and DCM. Portions of Na_2CO_3 were added until the pH of the aqueous phase reached 7.0. The DCM fraction was washed with water and saturated NaCl and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica-gel column chromatography (EtOAc:hexanes = 20:80) to give the title compound (120 mg, 56%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, J = 1.0, 7.9 Hz, 1H), 7.98 (d, J = 15.5 Hz, 1H), 7.85–7.78 (m, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.52 (ddd, J = 1.6, 6.7, 7.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.25 (ddd, J = 0.9, 2.2, 8.2 Hz, 1H), 7.10 (ddd, J = 0.9, 1.9, 7.9 Hz, 1H), 7.02 (t, J = 2.1 Hz, 1H), 6.46 (d, J = 15.5 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 150.5, 147.6, 142.4, 139.6, 138.4, 138.1, 135.2, 132.8, 131.5, 128.4, 127.8, 127.6, 127.5, 125.3, 123.1, 121.3, 120.5, 119.8, 118.7, 113.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{15}N_6O$, 391.1315; found, 391.1302.

(*E*)-3-(1-Carboxyethyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (109). The compound was synthesized according to the general procedure **D** from compound **40** with pyridine as solvent instead of acetic acid. The resulting mixture was concentrated *in vacuo* to give a yellow oil. The resulting oil was purified by silica gel column chromatography (DCM:methanol = 99:1) to give the title compound (29 mg, 16%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ

12.83 (br s, 1H), 8.12 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.99–7.90 (m, 3H), 7.87 (5-line multiplet, ω= 15.3 Hz, assigned as a ddd, *J* = 8, 7, 1.4 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 15.3 Hz, 1H), 7.54 (5-line multiplet, ω= 15.0 Hz, assigned as a ddd, *J* = 8, 7, 0.9 Hz, 1H), 5.55 (q, *J* = 6.7 Hz, 1H), 1.61 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.5, 161.2, 152.2, 147.3, 140.2, 139.2, 135.3, 133.1, 129.4, 127.6, 127.4, 126.7, 123.7, 120.8, 119.2, 112.0, 54.4, 15.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{16}N_3O_3$, 346.1186; found, 346.1193.

(*E*)-3-(2-Carboxyethyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (110). The compound was synthesized according to the general procedure **C** from compound **41**. The resulting mixture was concentrated to give a yellow precipitate. The precipitate was filtered and washed with EtOAc (5 mL, 3×) to give the title compound (209 mg, 40%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s,1H), 8.13 (d, *J* = 7.7 Hz, 1H), 8.10–8.00 (m, 2H), 9.00–7.88 (m, 3H), 7.87–7.78 (t, *J* = 7.2 Hz, 1H), 7.77–7.63 (m, 2H), 7.52 (t, *J* = 7.3 Hz, 1H) 4.49 (t, *J* = 7.2 Hz, 2H) 2.70 (t, *J* = 7.30 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 161.5, 152.2, 147.4, 140.3, 138.8, 135.0, 133.2, 129.3, 127.6, 127.2, 126.8, 123.9, 120.6, 119.2, 112.0, 33.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{16}N_3O_3$, 346.1186; found, 346.1178.

(*E*)-2-(4-Ethynylstyryl)-3-(3-sulfamoylphenyl)quinazolin-4(3*H*)-one (113). The compound was synthesized according to the general procedure **D** from compound **31**. The mixture was cooled to rt to produce a yellow precipitate. The precipitate was filtered and washed with water (3×) to give the title compound (210 mg, 31%) as yellow crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (ddd, *J* = 0.4, 1.5, 8.0Hz, 1H), 8.03 (ddd, *J* = 1.2, 1.8, 7.8 Hz, 1H), 7.96 (t, *J* = 1.7 Hz, 1H), 7.95–7. 88 (m, 2H), 7.87–7.78 (m, 2H), 7.76 (ddd, *J* = 1.1, 2.0, 7.9 Hz, 1H), 7.61–7.54 (m, 3H), 7.46 (br d, *J* = 8.4 Hz, 2H), 7.41 (br d, *J* = 8.4 Hz, 2H), 6.34 (d, *J* = 15.5 Hz, 1H), 4.34 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 151.2, 147.8, 146.0, 138.7, 137.7, 135.6, 135.4, 132.8, 133.1, 131.1, 128.29, 127.8, 127.4, 127.0, 126.9, 126.8, 123.4, 121.2, 121.1, 83.7, 83.3. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{17}N_3O_3S$, 428.1063; found, 428.1068.

(*E*)-3-(3-Carboxyphenyl)-2-(4-cyanophenethyl)quinazolin-4(3*H*)-one (114). To a 50-mL oven-dried round-bottom flask was **1** (100 mg, 0.25 mmol) dissolved in a mixture of EtOAc and ethanol (50:50, 25 mL). The flask was purged with argon gas before catalytic amount of 10% Pd/C (18 mg) was added. The resulting system was then flushed with hydrogen gas. The mixture was stirred at rt for 8 h under positive pressure of hydrogen gas. Then, the reaction mixture was filtered over celite, the filtrate was collected, and the solvent was removed under reduced pressure giving the desired compound (85 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.65 (m, 2H), 3.13 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.55–7.64 (m, 3H), 7.69 (m, 2H), 7.74 (dd, *J* = 7.6 Hz, 0.80 Hz, 1H), 7.88–7.93 (m, 2H), 8.05 (m, 1H), 8.15 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.7, 162.3, 156.3, 147.8 (2C), 137.3, 135.5, 133.0 (3C), 132.1, 130.6, 130.3 (3C), 130.1 (2C), 127.8, 127.5, 127.2, 121.4, 119.8, 37.0, 32.6. HRMS (ESI$^+$) *m/z* calc. $C_{24}H_{18}N_3O_3^+$ $[M + H]^+$: 396.1343, found: 396.1356.

(*E*)-3-(3-Carboxyphenyl)-2-(4-fluorophenethyl)quinazolin-4(3*H*)-one (115). (*E*)-3-(3-Carboxyphenyl)-2-(4-fluorostyryl)quinazolin-4(3*H*)-one **115a** (100 mg, 0.26 mmol) was dissolved in a mixture of EtOAc and ethanol (50:50, 37 mL) under an atmosphere of argon. This was followed by adding 10% Pd/C (18 mg) and the system was flushed with hydrogen. The mixture was stirred at rt for 8 h under positive pressure of hydrogen in a balloon. The

reaction mixture was filtered over celite, the filtrate was evaporated to dryness *in vacuo* to give the title compound (88 mg, 87%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, J = 8.00 Hz, 1.2 Hz, 1H), 8.05 (m, 1H), 7.89-7.93 (m, 2H), 7.77 (d, J = 7.70 Hz, 1H), 7.53–7.64 (m, 3H), 7.13 (m, 2H), 7.05 (m, 2H), 3.01 (m, 2H), 2.61 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.1, 162.5, 161.7 (d, J_{CF} = 242.4 Hz, 1C), 156.9, 148.1, 138.0, 137.9, 135.8, 132.1, 131.1, 131.0, 130.8, 130.4, 130.3, 128.0, 127.7, 127.4, 121.5, 116.1 (d, J_{CF} = 21.2 Hz, 1C), 38.3, 32.1. HRMS (ESI$^+$) *m/z* calc. $C_{23}H_{18}FN_2O_3^+$ [M + H]$^+$: 389.1296, found: 389.1305.

(*E*)-2-((4-Cyanobenzyl)amino)-3-(3-methoxycarbonylphenyl)quinazolin-4(3*H*)-one (116). To a 10 mL tube were **43** (50 mg, 0.16 mmol) and 4-aminomethylbenzonitrile (25 mg, 1.6 mmol) dissolved in 5 mL of THF with triethylamine (16 mg, 22 μL, 0.16 mmol). The resulting mixture was heated at 100 °C for 2 h. The residue reagent was removed before addition of 10 mL of EtOAc and 10 mL 5% citric acid aqueous solution. The aqueous solution was washed with EtOAc (3×). The organic layers were combined and concentrated *in vacuo* and purified by silica gel column chromatography (DCM:MeOH = 99:1) to give the title compound (9 mg, 14%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (t, J = 3.7 Hz, 1H), 8.01 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.84–7.71 (m, 4H), 7.61 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H), 4.63 (dd, J = 5.6, 16.1 Hz, 1H), 4.51 (dd, J = 5.8, 16.1 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.1, 162.2, 150.3, 146.4, 135.8, 135.0, 134.8, 132.6, 132.0, 131.2, 130.8, 130.6, 128.3, 127.0, 124.9, 122.6, 119.4, 117.5, 109.7, 52.9, 44.6. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{24}H_{19}N_4O_3$, 411.1452; found, 411.1463.

(*E*)-2-((4-Fluorobenzyl)amino)-3-(3-methoxycarbonylphenyl)quinazolin-4(3*H*)-one (117). Following the synthesis protocol of compound **116**, compound **117** was synthesized and purified by preparative thin layer chromatography (EtOAc:hexanes = 50/50) to give the title compound (20 mg, 12%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br d, J = 7.8 Hz, 1H), 8.07 (dd, J = 1.3, 7.9 Hz, 1H), 7.99 (t, J = 1.6 Hz, 1H), 7.67–7.59 (m, 2H), 7.54–7.43 (m, 2H), 7.26 (d, J = 5.4 Hz, 1H), 7.24 (d, J = 5.4 Hz, 1H), 7.22–7.16 (m, 1H), 6.96 (t, J = 8.7 Hz, 2H), 4.66 (dd, J = 5.7, 14.9 Hz, 1H), 4.60–4.46 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 162.5, 162.1 (d, J_{CF} = 246.2 Hz, 1C), 148.9, 134.9, 134.2, 133.4, 132.7, 131.0, 130.7, 130.3, 129.43, 129.35, 127.2, 125.1, 123.0, 117.5, 115.6, 115.4, 52.5, 44.9. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{23}H_{19}FN_3O_3$, 404.1405; found, 404.1419.

(*E*)-3-(3-Carbonylphenyl)-2-((4-cyanobenzyl)amino)quinazolin-4(3*H*)-one (118). Compound **116** (100 mg, 0.24 mmol) was dissolved in a mixture of MeOH and H_2O (10:1). Excessive LiOH (58 mg, 2.44 mmol) was dispersed in the solution and the mixture was stirred overnight. After confirmation by TLC for completion of the reaction, the mixture was treated with HCl (aq.) until pH = 7. The residual solvent was removed under reduced pressure until a white precipitate appeared. The precipitate was then triturated with diethyl ether to give the title compound (42 mg, 43%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 8.09 (d, J = 7.6 Hz, 1H), 7.94–7.88 (m, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.68 (t, J = 7.7 Hz, 1H), 7.64–7.56 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 6.66 (t, J = 6.0 Hz, 1H), 4.62 (dd, J = 16.0, 5.9 Hz, 1H), 4.52 (dd, J = 16.0, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.9, 161.9, 150.0, 149.4, 146.1, 134.90, 134.89, 134.5, 132.1, 130.18, 130.16, 127.9, 126.51, 126.49, 124.7, 122.0, 119.0, 117.1, 109.2, 44.2. HRMS-ESI (*m/z*): [M + H]$^+$ calcd for $C_{23}H_{17}N_4O_3$, 397.1295; found, 397.1305.

(*E*)-2-((4-Cyanobenzyl)amino)-3-(3-nitrophenyl)quinazolin-4(3*H*)-one (119). Compound **47** (1.08 g, 3.59 mmol) and 4-aminomethylbenzonitrile (523 mg, 3.59 mmol) were dissolved in 5 mL of pyridine in a 25-mL round-bottom flask. The mixture was heated under reflux for 2 h. The resulting solution was washed with 20 mL 5% citric acid, filtered and washed with cold EtOAc (3×). The filtrate was concentrated *in vacuo* and the residue was purified by silica-gel column chromatography (DCM:methanol = 90:10) to give **119** (71 mg, 5%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (ddd, *J* = 1.0, 2.1, 8.2 Hz, 1H), 8.20 (t, *J* = 1.9 Hz, 1H), 8.05 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.69 (ddd, *J* = 1.1, 1.8, 7.9 Hz, 1H), 7.64 (ddd, *J* = 1.5, 7.3, 8.1 Hz, 1H), 7.53 (br d, *J* = 8.3 Hz, 2H), 7.45–7.36 (m, 3H), 7.21 (5-line multiplet, ω= 15.2 Hz, assigned as a ddd, *J* = 8, 7, 1.0 Hz, 1H), 4.74 (dd, *J* = 8.1, 17.3 Hz, 1H), 4.69–4.60 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) 162.4, 149.4, 148.9, 148.2, 144.1, 135.8, 135.5, 135.3, 132.4, 131.6, 128.2, 127.2, 125.4, 124.9, 124.8, 123.5, 118.7, 117.4, 111.1, 45.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{16}N_5O_3$, 398.1248; found, 398.1248.

(*E*)-2-((4-Fluorobenzyl)amino)-3-(3-nitrophenyl)quinazolin-4(3*H*)-one (120). Following the synthesis of **119**, 938 mg of **47** was used to give the title compound (474 mg, 39%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 8.45 (t, *J* = 1.8 Hz, 1H), 8.42 (ddd, *J* = 1.2, 2.3, 8.0 Hz, 1H), 7.95 (ddd, *J* = 1.3, 1.8, 7.9 Hz, 1H), 7.92 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.91 (td, *J* = 0.5, 8.0 Hz, 1H), 7.66–7.59 (m, 1H), 7.40–7.33 (m, 2H), 7.29 (dd, *J* = 0.5, 8.2 Hz, 1H), 7.13–7.05 (m, 2H), 6.69 (t, *J* = 6.0 Hz, 2H), 4.56 (dd, *J* = 6.0, 15.4 Hz, 1H), 4.53 (dd, *J* = 5.8, 15.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) 44.0, 115.2 (d, J_{CF} = 21.2 Hz, 1C), 117.5, 122.4, 124.9, 125.2, 125.7, 126.9, 129.5 (d, J_{CF} = 8.0 Hz, 1C), 132.0, 135.1, 136.4 (d, J_{CF} = 2.9 Hz, 1C), 136.8, 137.1, 149.5, 150.1, 150.2, 161.5 (d, J_{CF} = 241.9 Hz, 1C), 162.3. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{16}N_4O_3$, 391.1201; found, 391.1265.

(*E*)-3-(3-Aminophenyl)-2-((4-cyanobenzyl)amino)quinazolin-4(3*H*)-one (121). To a solution of **119** (300 mg, 0.75 mmol) in 10 mL of ethanol was added tin(Ⅱ) chloride (429 mg, 2.26 mmol) at rt. A few drops of concentrated 12 N HCl (aq.) was then added and the mixture was heated at reflux for 2 h. The resulting mixture was concentrated *in vacuo* to give a brown oil. The oil was taken up in EtOAc (20 mL). The organic phase was washed with water (20 mL). The aqueous layer was collected and washed with EtOAc (10 mL, 2×). A portion of NH_4OH (aq.) was then added dropwise to the aqueous layer until pH reached 8.0. The aqueous solution was then washed with EtOAc (10 mL, 3×). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (220 mg, 79%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.64–7.57 (m, 3H), 7.42–7. 35 (m, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.78 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.58 (t, *J* = 1.9 Hz, 1H), 4.82–4.70 (m, 2H), 4.65 (dd, J=7.4, 17.3 Hz, 1H), 3.99 (br s, 2H). ^{1}H NMR (500 MHz, $CDCl_3$ + D_2O) δ 8.13 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.65–7.56 (m, 3H), 7.41–7.35(m, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.22–7.16 (m, 1H), 6.79 (ddd, *J* = 0.8, 2.2, 8.2 Hz, 1H), 6.65 (ddd, *J* = 0.8, 1.9, 7.7 Hz, 1H), 6.58 (t, *J* = 2.1 Hz, 1H), 4.71(ABq, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 16.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 149.4, 149.2, 149.1, 144.6, 135.7, 134.9, 132.6, 131.7, 128.2, 127.5, 125.2, 123.2, 119.0, 118.1, 117.9, 116.8, 114.9, 111.3, 45.1. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{18}N_5O$, 368.1506; found, 368.1506.

(*E*)-3-(3-Aminophenyl)-2-((4-fluorobenzyl)amino)quinazolin-4(3*H*)-one (122). To a solution of **120** (100 mg, 0.26 mmol) in 10 mL of ethanol was added Tin(Ⅱ) chloride (146

mg, 0.77 mmol) at rt. A few drops of concentrated 12 N HCl (aq.) was then added and the mixture was heated at reflux for 3.5 h. The solvent was removed to give yellow oil. The oil was diluted with EtOAc and washed with 5% ammonia solution (aq.). The EtOAc layers were collected and concentrated *in vacuo* to give yellow oil. The yellow oil was purified via preparative TLC plate (EtOAc/hexanes = 1/1, 2×) to give the title compound (48 mg, 52%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.1 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.33–7.21 (m, 3H), 7.18 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 8.6 Hz, 2H), 6.72 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 6.57 (br s,1H), 4.79 (br s,1H), 4.69 (d, J = 14.8 Hz, 1H), 4.55 (d, J = 14.7 Hz, 1H), 3.97 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 44.9, 114.9, 115.6 (d, J_{CF} = 21.4 Hz, 1C), 116.6, 117.8, 122.9, 124.9, 127.3, 129.3 (d, J_{CF} = 8.0 Hz, 1C), 129.4, 131.4, 134.3 (d, J_{CF} = 2.7 Hz, 1C), 134.8, 135.0, 135.5, 149.0, 149.5, 162.2 (d, J_{CF} = 245.4 Hz, 1C), 162.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -115.07 (s, 1F). HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{20}FN_4O_2$, 403.1565; found, 403.1577.

(*E*)-2-((4-Cyanobenzyl)amino)-3-(3-methylsulfonamidophenyl)quinazolin-4(3*H*)-one (123). Compound **121** (80 mg, 0.22 mmol) was dissolved in 2 mL pyridine at ice-water temperature. Mesyl chloride (0.85 mL, 1.10 mmol) was then added dropwise. The mixture was refluxed for 3 hrs. The reaction was quenched by the addition of 100 mL of 5% citric acid. The resulting white suspension was filtered and the solid was washed with water (3×), hexanes (3×) and diethyl ether (3×) to give the title compound (75 mg, 77%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s,1H), 7.91 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.20–7.09 (m, 2H), 6.78 (br s, 1H), 4.59 (d, J = 5.1 Hz, 2H), 3.07 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 150.4, 146.4, 140.6, 135.9, 135.1, 132.6, 131.5, 128.3, 127.0, 124.9, 124.7, 122.73, 122.69, 121.1, 120.1, 119.4, 117.4, 109.8, 44.6, 39.9. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{20}N_5O_3S$, 446.1281; found, 446.1265.

(*E*)-2-(Benzylthio)-3-(3-carboxyphenyl)quinazolin-4(3*H*)-one (124). Compound **43** (200 mg, 0.67 mmol) was dissolved in 2 mL of anhydrous DMF in an oven-dried flask, at which time NaH (90 mg, 1.68 mmol) was dispensed into the solution and the mixture was stirred for 30 mins. Benzyl bromide was added and the resulting mixture was stirred at rt for 8 h. The reaction was quenched by the addition of iced water to give a white suspension, which was filtered. The solid was washed with water and the filtrate was acidified by 1 N HCl to pH = 4. The aqueous layer was washed with EtOAc (3×). The combined organic layer was washed sequentially with water and brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give the title compound (135 mg, 52%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.32 (s, 1H), 8.09 (dd, J = 1.3, 7.7 Hz, 2H), 7.99 (t, J = 1.6 Hz, 1H), 7.91–7.82 (m, 1H), 7.77–7.64 (m, 3H), 7.54–7.46 (m, 1H), 7.46–7.39 (m, 2H), 7.33–7.19 (m, 3H), 4.43 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 13.2 Hz, 2H).^{13}C NMR (126 MHz, DMSO-d_6) δ 166.9, 161.3, 156.9, 147.7, 137.1, 136.6, 135.5, 134.4, 132.8, 131.1, 130.8, 130.4, 129.8, 128.9, 127.8, 127.1, 126.6, 126.5, 120.1, 36.4. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3S$, 389.0954; found, 389.0939.

(*E*)-3-(3-Carboxyphenyl)-2-((4-cyanobenzyl)thio)quinazolin-4(3*H*)-one (125). Compound **44** (223 mg, 714 μmol) was dissolved in 2 mL anhydrous DMF in a 10-mL round-bottom flask. Sodium hydride (57 mg, 1.43 mmol) was added and the mixture was stirred

for 1 h at rt. 4-(Bromomethyl)benzonitrile (140 mg, 714 μmol) was then added and the resulting mixture was stirred at rt for 8 h. Iced water (10 mL) was added to quench the reaction. The resulting suspension was filtered, and the filtrate was acidified by 1 N HCl to a state of pH = 4, which resulted in a white precipitate. The precipitate was filtered and the solid was washed with water to give the title compound (196 mg, 66%) as a white solid. ^{1}H NMR (500 MHz, DMSO) δ 13.19 (s, 1H), 8.13–8.03 (m, 2H), 7.99 (s, 1H), 7.85 (t, J = 7.0 Hz, 1H), 7.80–7.71 (m, 3H), 7.71–7.60 (m, 4H), 7.48 (t, J = 7.4 Hz, 1H), 4.47 (ABq, $\Delta\delta_{AB}$ = 0.02 , J_{AB} = 14.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.2, 160.6, 155.8, 146.9, 143.3, 135.9, 134.8, 133.9, 132.12, 132.05, 130.5, 130.2, 129.8, 126.4, 125.97, 125.95, 119.5, 118.6, 109.76, 109.75, 35.0. HRMS (ESI$^+$) *m/z* calc. $C_{23}H_{16}N_3O_3S$ $[M+H]^+$: 414.0907, found: 414.0908.

(*E*)-3-(3-Carboxyphenyl)-2-((4-cyanobenzyl)oxy)quinazolin-4(3*H*)-one (126). To a 10 mL flask were **44** (44 mg, 0.16 mmol) and 60% NaH (16 mg, 0.39 mmol) dissolved in 2 mL DMF. The mixture was stirred at rt for 20 mins before a solution of 4-(bromomethyl)benzonitrile (31 mg, 0.16 mmol) in DMF (2 mL) was added. The mixture was then stirred for another 2 h at rt before being poured into crushed ice (10 g). The resulting mixture was then acidified by 1N HCl (aq.) and washed with EtOAc (5 mL, 3×). The organic layers were combined, washed by water (40mL, 3×) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give white solid, which was further purified by preparative TLC plate (EtOAc:hexanes = 1:1) to give the title compound (11 mg, 17%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 8.11 (dd, J = 1.6, 7.8 Hz, 1H), 8.04 (t, J = 1.6 Hz, 1H), 8.02 (td, J = 1.5, 7.5 Hz, 1H), 7.84 (s, 1H), 7.82 (s, 1H), 7.74–7.67 (m, 2H), 7.67–7.61 (m, 3H), 7.32 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 5.48 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 161.9, 151.4, 142.7, 140.3, 137.0, 134.0, 135.9, 133.0, 132.3, 130.7, 129.6, 128.7, 128.1, 123.5, 119.2, 116.5, 115.4, 110.6, 46.8. ^{13}C NMR (101 MHz, $CDCl_3$) 170.6, 161.7, 151.5, 141.2, 140.0, 136.1, 135.7, 134.1, 133.1, 131.1, 130.89, 130.73, 130.0, 129.9, 127.6, 124.1, 118.6, 116.2, 114.4, 112.1, 47.5. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{16}N_3O_4$, 398.1135; found, 398.1134.

3-(3-Nitrophenyl)-2-(piperidin-1-yl)quinazolin-4(3*H*)-one (127). Compound **47** (260 mg, 0.86 mmol), excessive piperidine (367 mg, 4.31 mmol) and triethylamine (1 mL) in THF (10 mL) were added to a pressure vessel at rt. The vessel was sealed, and the mixture was heated up to 110 ˚C for 8 h. The residue was concentrated *in vacuo* to give brown solid. The solid was then triturated with limited amount of cold EtOAc (5 mL) to give the title compound (251 mg, 83%) as a white crystal. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (t, J = 2.1 Hz, 1H), 8.30 (ddd, J = 1.0, 2.3, 8.3 Hz, 1H), 8.03 (ddd, J = 0.5, 1.6, 8.0 Hz, 1H), 8.01 (ddd, J = 1.0, 1.9, 8.0 Hz, 1H), 7.81 (t, J = 8.1 Hz, 1H), 7.76 (ddd, J = 1.6, 8.2, 7.1 Hz, 1H), 7.52 (ddd, J = 0.5, 1.1, 8.2 Hz, 1H), 7.37 (ddd, J = 1.1, 7.2, 7.9 Hz, 1H), 3.00 (t, J = 5.3 Hz, 4H), 1.42–1.28 (m, 2H), 1.21–1.07 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.6, 154.7, 148.10, 148.07, 138.9, 136.6, 135.4, 130.2, 127.2, 126.4, 125.1, 125.1, 123.2, 119.3, 50.2, 25.0, 24.0. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{19}N_4O_3$, 351.1452; found, 351.1449.

3-(3-Aminophenyl)-2-(piperidin-1-yl)quinazolin-4(3*H*)-one (128). To a solution of **126** (200 mg, 0.57 mmol) in a mixture of DCM, methanol and ethanol (40:10:50, 20 mL) was added Tin(Ⅱ) chloride (974 mg, 5.14 mmol) at rt. A few drops of concentrated HCl (12 N) was then added and the mixture was heated at reflux for 1.5 h. The mixture was basified with sodium hydroxide solution (1 N) to give a white precipitate (pH = 8). The precipitate was

filtered off to give clear brown filtrate, which was concentrated *in vacuo* to give brown oil. The brown oil was purified via silica gel column chromatography (EtOAc:hexanes = 30:70) to give the title compound (15 mg, 8%) as a yellow powder. ^{1}H NMR (500 MHz, DMF-d_7) δ 8.08–8.03 (m, 1H), 7.77–7.70 (m, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 6.80–6.69 (m, 2H), 6.63 (td, J = 0.9, 7.8 Hz, 1H), 5.38 (s, 2H), 3.17 (t, J = 5.2 Hz, 4H), 1.50–1.38 (m, 2H), 1.37–1.25 (m, 4H). ^{13}C NMR (126 MHz, DMF-d_7) δ 162.2, 154.6, 149.2, 147.9, 138.4, 133.9, 128.3, 126.3, 125.3, 123.4, 118.7, 116.0, 114.3, 112.9, 49.4, 24.4, 23.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{21}N_4O$, 321.1710; found, 321.1707.

2-(4-(4-Chlorophenyl)piperazin-1-yl)-3-(3-nitrophenyl)-quinazolin-4(3*H*)-one (129a). To a 15 mL tube were **47** (0.74 g, 2.44 mmol), 1-(4-chlorophenyl)piperazine (0.48 g, 2.44 mmol) and triethylamine (0.49 g, 0.68 mL, 4.88 mmol) dissolved in 5 mL of THF. The tube was sealed, and the mixture was heated at 110 °C for 12 h before being allowed to cool down. The reaction was quenched by 10 mL of 2% NaOH(aq.), washed by EtOAc (20 mL, 2×). The organic layers were combined and washed with water (3×). The 12N HCl (aq) was then added dropwise to the organic phase with stirring on, which resulted in a white precipitate. The precipitate was filtered to give 0.90 g of the title compound in hydrogen chloride salt form, a white solid, as crude product without purification. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{21}N_5O_3Cl$, 462.1327; found, 462.1305.

3-(3-Aminophenyl)-2-(4-(4-chlorophenyl)piperazin-1-yl)quinazolin-4(3*H*)-one (129). To **128a** (0.40 g, 0.75 mmol) in a mixture of ethanol, methanol and DCM (50:20:30, 20 mL) was Tin (Ⅱ) chloride (0.99 g, 5.22 mmol) added. A few drops of 12N HCl (aq.) was then added. The mixture was then heated under reflux for 2 h. The pH was adjusted to 8.0 by the addition of saturated $NaHCO_3$ solution , which resulted in a white precipitate. The precipitate was filtered to give a clear filtrate. The aqueous layer was separated and its pH was adjusted to 4.0 by addition of 1N HCl (aq.). The solution was washed with EtOAc (20 mL, 3×). The EtOAc layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound (0.27 g, 83%) as an off-white powder. ^{1}H NMR (400 MHz, DMF-d_7) δ 8.10 (dd, J = 1.2, 7.9 Hz, 1H), 7.82 (ddd, J = 1.6, 7.2, 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.59–7.51 (m, 2H), 7.49–7.37 (m, 3H), 7.28 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 3.40 (t, J = 4.6 Hz, 4H), 3.09 (br s, 4H). ^{13}C NMR (126 MHz, DMF-d_7) δ 162.6, 154.4, 149.7, 147.4, 139.3, 138.7, 135.3, 130.0, 129.3, 127.3, 125.8, 125.4, 125.3, 121.7, 120.7, 119.5, 118.1, 105.0, 49.1, 48.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{23}ClN_5O$, 432.1586; found, 432.1598.

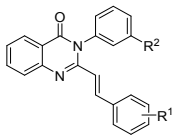
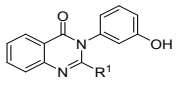
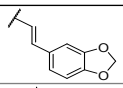
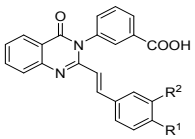
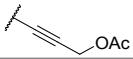
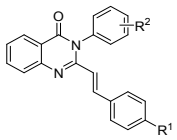
Table S1. MIC of reported compounds against the ESKAPE organisms

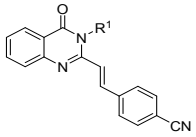
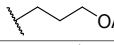
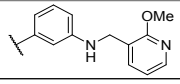
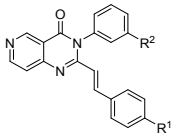
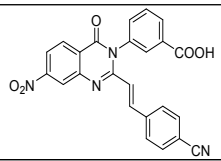
Compds	*ESKAPE* panel					
	E. faecium NCTC 7171	*S. aureus* ATCC 29213	*K. pneumoniae* ATCC 700603	*A. baumanii* ATCC 17961	*P. aeruginosa* ATCC 27853	*E. aerogenes* ATCC 35029
1	> 128	2	> 128	> 128	> 128	> 128

48	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
49	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
50	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
51	> 128	32	> 128	> 128	> 128	> 128
52	> 128	8	> 128	> 128	> 128	> 128
53	128	0.5	> 128	> 128	> 128	> 128
54	> 128	0.25	> 128	> 128	> 128	> 128
55	> 128	4	> 128	> 128	> 128	> 128
56	> 128	4	> 128	> 128	> 128	> 128
58	> 128	0.25	> 128	> 128	> 128	> 128
59	> 128	0.5	> 128	> 128	> 128	> 128
60	> 128	64	> 128	> 128	> 128	> 128
61	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
62	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
63	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
64	> 128	64	> 128	> 128	> 128	> 128
65	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
66	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
67	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
68	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
69	> 64	8	> 64	> 64	> 64	> 64
70	> 128	64	> 128	> 128	> 128	> 128
71	> 128	16	> 128	> 128	> 128	> 128
72	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
73	> 128	0.5	> 128	> 128	> 128	> 128
74	> 128	2	> 128	> 128	> 128	> 128
75	> 128	2	> 128	> 128	> 128	> 128
76	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
77	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
78	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
79	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
80	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
81	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
82	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
83	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
84	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
85	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
86	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
87	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
88	> 128	2	> 128	> 128	> 128	> 128
89	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
90	16	8	> 128	> 128	> 128	> 128
91	> 128	32	> 128	> 128	> 128	> 128
92	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
93	> 128	16	> 128	> 128	> 128	> 128
94	> 128	0.25	> 128	> 128	> 128	> 128

95	> 128	4	> 128	> 128	> 128	> 128
96	> 128	2	> 128	> 128	> 128	> 128
97	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
98	> 128	32	> 128	> 128	> 128	> 128
99	> 128	0.5	> 128	> 128	> 128	> 128
100	> 128	0.015	> 128	> 128	> 128	> 128
101	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
102	> 128	32	> 128	> 128	> 128	> 128
103	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
104	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
105	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
106	> 128	2	> 128	> 128	> 128	> 128
107	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
108	> 128	16	> 128	> 128	> 128	> 128
109	n.d.	128	n.d.	n.d.	n.d.	n.d.
110	n.d.	> 128	n.d.	n.d.	n.d.	n.d.
113	> 128	0.06	> 128	> 128	> 128	> 128
114	> 128	8	> 128	> 128	> 128	> 128
115	> 128	2	> 128	> 128	> 128	> 128
116	> 128	16	> 128	> 128	> 128	> 128
117	n.d.	>128	n.d.	n.d.	n.d.	n.d.
118	n.d.	>128	n.d.	n.d.	n.d.	n.d.
119	n.d.	>128	n.d.	n.d.	n.d.	n.d.
120	n.d.	>128	n.d.	n.d.	n.d.	n.d.
121	> 128	8	> 128	> 128	> 128	> 128
122	n.d.	64	n.d.	n.d.	n.d.	n.d.
123	> 128	0.125	> 128	> 128	> 128	> 128
124	> 128	0.25	> 128	> 128	> 128	> 128
125	> 128	2	> 128	> 128	> 128	> 128
126	n.d.	>128	n.d.	n.d.	n.d.	n.d.
127	n.d.	>128	n.d.	n.d.	n.d.	n.d.
128	n.d.	>128	n.d.	n.d.	n.d.	n.d.
129	n.d.	>128	n.d.	n.d.	n.d.	n.d.

Table S2. Additional compounds used in the QSAR study

Compounds and data from the previous work[4]				
Core structures	R^1	R^2	QSAR set	MIC[a] (μg/mL)
	4-NO_2	OH	test	2
	4-CN	CO_2H	training	2
	2-NO_2	OH	training	128
	4-F	OH	training	0.25
	3-F	OH	test	1
	2-F	OH	training	1
	4-Cl	OH	training	0.125
	4-Me	OH	training	0.25
	4-OMe	OH	training	4
	4-acetylene	OH	training	0.003
	4-CO_2H	OH	training	> 128
	H	OH	training	0.5
		-	training	2
		-	training	2
		-	training	128
		-	training	0.06
		-	training	0.06
		-	training	128
	acetylene	H	training	0.03
		H	training	0.25
	F	H	test	1
	F	F	training	2
	F	Cl	training	2
	Ms	H	test	> 128
	NO_2	2-OH	training	2
	NO_2	4-OH	training	>128
	NO_2	3-OAc	training	>128
	NO_2	4-OAc	training	>128
	F	3-OMe	test	>128
	F	3-NO_2	training	>128
	F	3-NH_2	training	2
	F	3-NHAc	training	1

	F	3-NHMs	test	0.125
	F	3-$CONH_2$	training	4
	F	3-$CONHC_2H_4OH$	training	2
	CN	3-CH_2OAc	training	0.03
	CN	3-F	training	>128
	CN	3-NO_2	test	>128
	CN	3-NH_2	training	0.5
	CN	3-NH*i*Pr	training	0.01
	CN	3-NHAc	training	0.25
	CN	3-CH_2NHAc	test	0.015
	CN	3-NHMs	test	0.004
	CN	3-CH_2NHMs	test	4
	CN	3-$NHCO_2Me$	test	0.5
	CN	3-$CONHC_2H_4OH$	training	1
		-	training	>128
		-	training	0.5
		-	training	2
	Cl	OH	training	1
	CN	OH	test	0.5
	CN	CO_2H	training	>128
	F	$CONH_2$	training	>128
	Cl	$CONH_2$	test	>128
	CN	$CONH_2$	training	>128
	-	-	training	>128

Compounds from the present work

QSAR sets	Compound codes
Test	**67**, **68**, **74**, **82**, **92**, **101**, **108**, **126**.
Training	**49**, **50**, **53**, **54**, **58**, **62**, **63**, **65**, **66**, **72**, **73**, **75**, **76**, **77**, **78**, **79**, **80**, **81**, **84**, **85**, **86**, **87**, **88**, **94**, **95**, **97**, **99**, **103**, **105**, **106**, **107**, **109**, **110**, **119**, **123**, **124**, **125**, **126**, **128**.

[a] *S. aureus* ATCC29213 strain

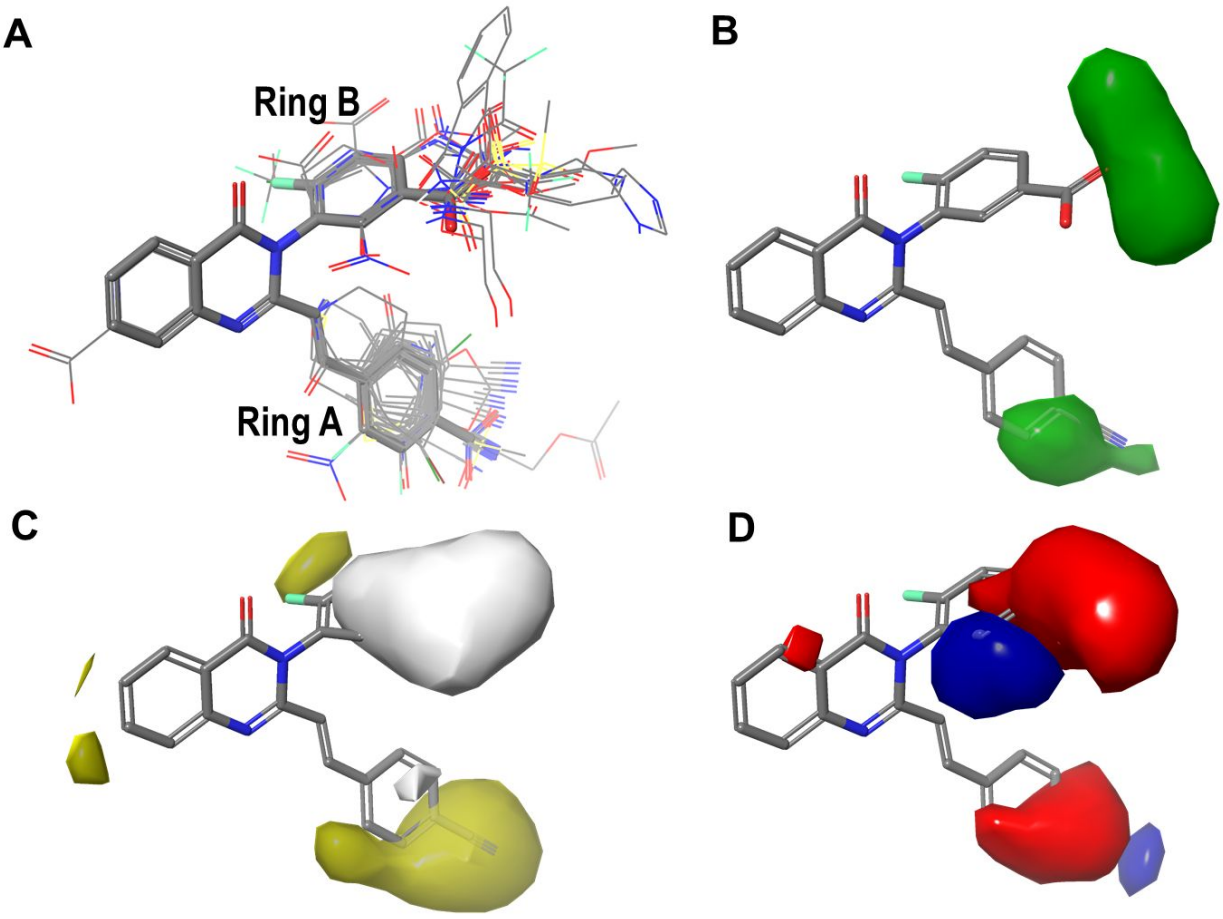


Figure S2. Computational analysis of the quinazolinones. (A) Alignment of all the 103 quinazoliones [compounds reported herein and previously published[4] (Table S1)] used for generating the 3D-QSAR model. Compound **73** is displayed in capped-stick representation, while all other compounds are in line representation. The ring designations are labeled. The model with four PLS factors provided a correlation coefficient (r^2) of 0.80 between the predicted and experimental MIC with the training data set (84 compounds). For internal validation, leave-one-out method provided a cross-validated r^2 (r^2_{cv}) of 0.42. The external validation with the test dataset (21 compounds), which were not used in the model building, gave a correlation coefficient of 0.44 between predicted and experimental activities.(B) Steric contour map generated shows the steric-bulk favored region in dark green color. (C) Hydrophobic map shows hydrophobic preferred (green) and hydrophilic-preferred (white) regions. (D) Electrostatic contour maps represented in blue (electropositive region) and red (electronegative region).

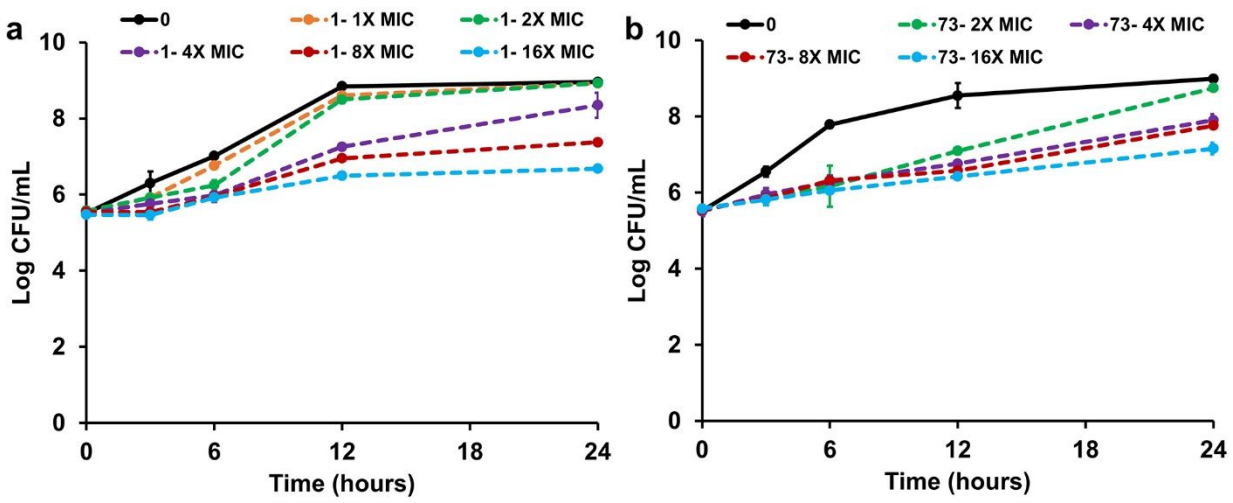


Figure S3. Time-kill assays for (a) compound 1 and (b) compound 73 at MICs ranging from 1× to 16× MIC.

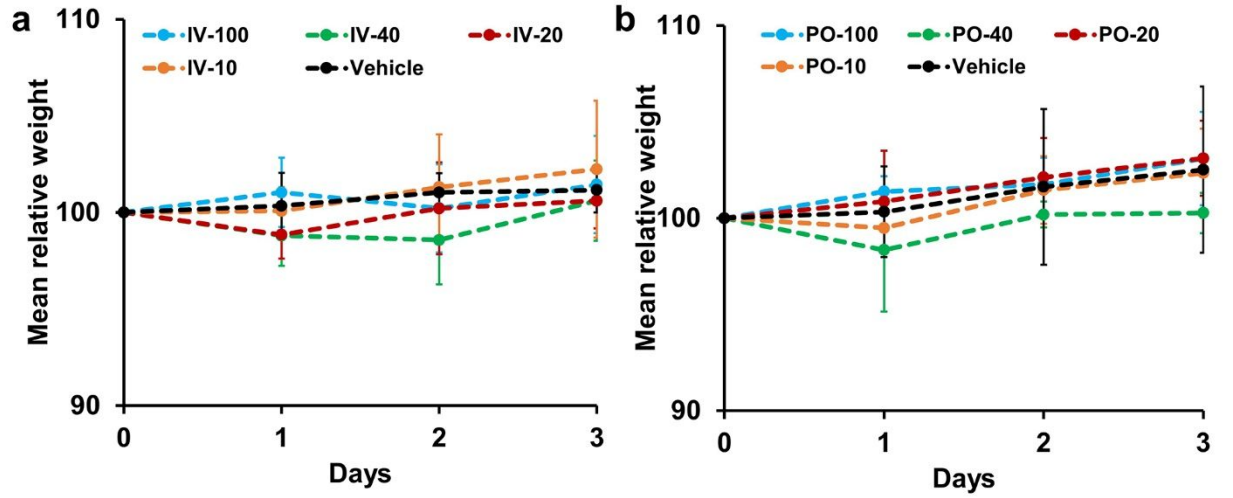
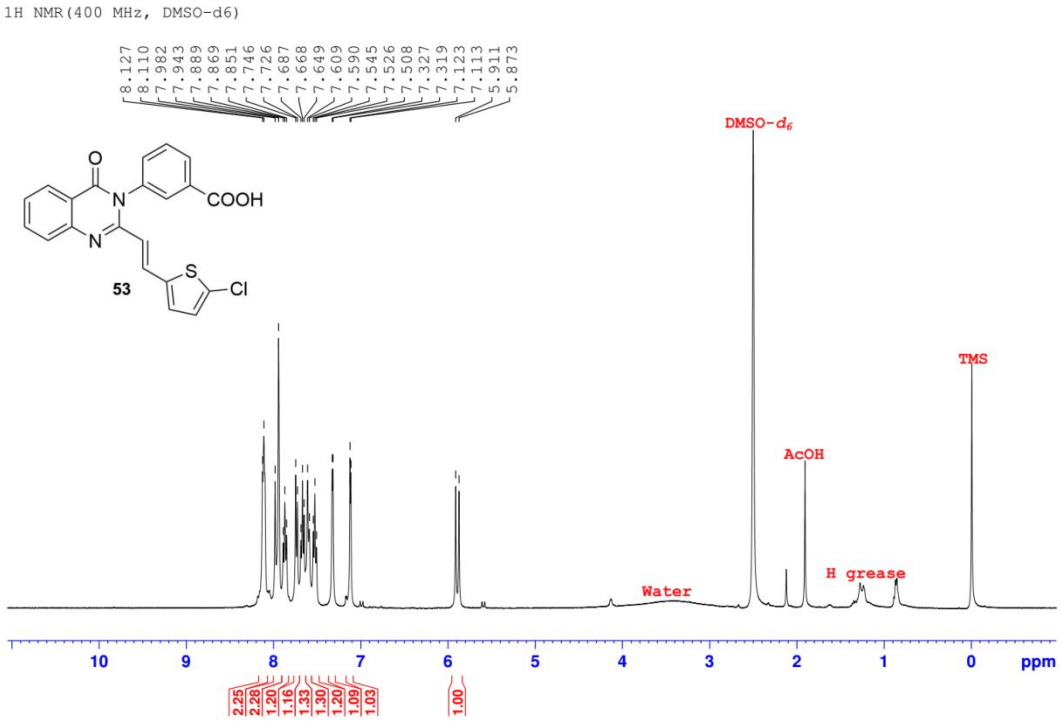
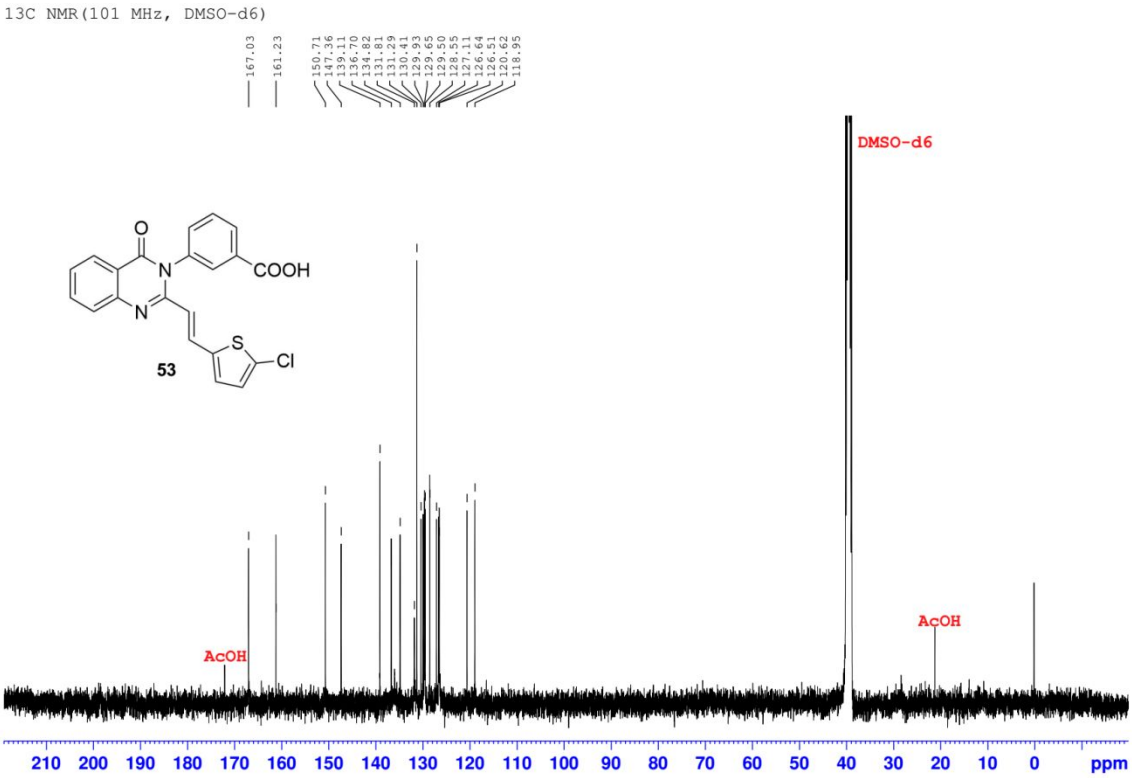


Figure S4. Dose tolerance of compound 73 after (a) single intravenous dose administration at 10, 20, 40, and 100 mg/kg and (b) single oral doses at 10, 20, 40, and 100 mg/kg. A vehicle control (5% DMSO/95% water) was included. N = 4 mice/group. No loss of body weight was observed and the mice had normal urine and feces output and behaved normally.

Representative NMR spectra/LCMS results

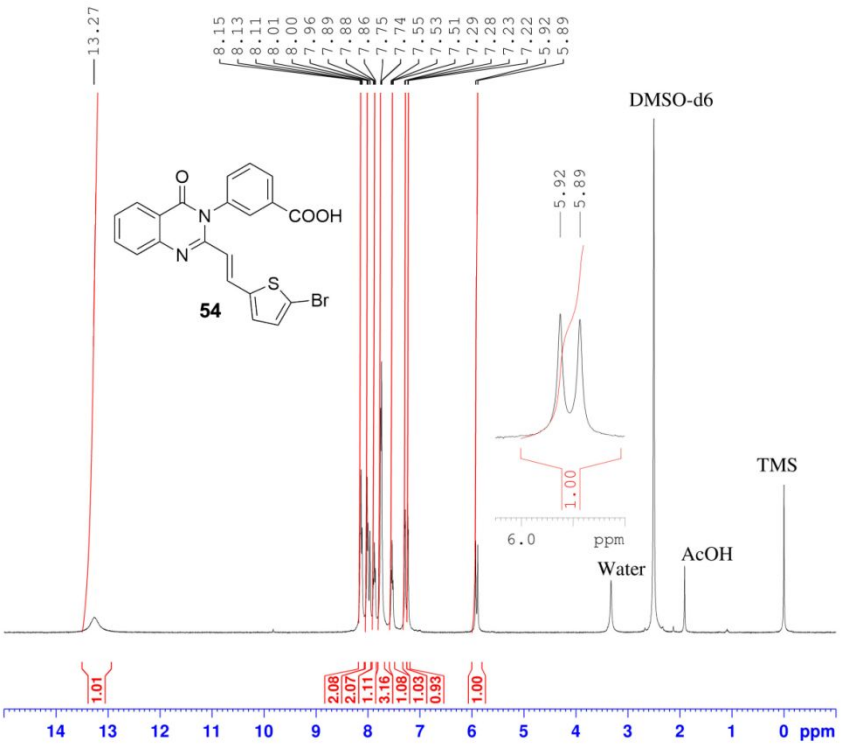
(*E*)-3-(3-Carboxyphenyl)-2-(2-(5-chlorothiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (53).



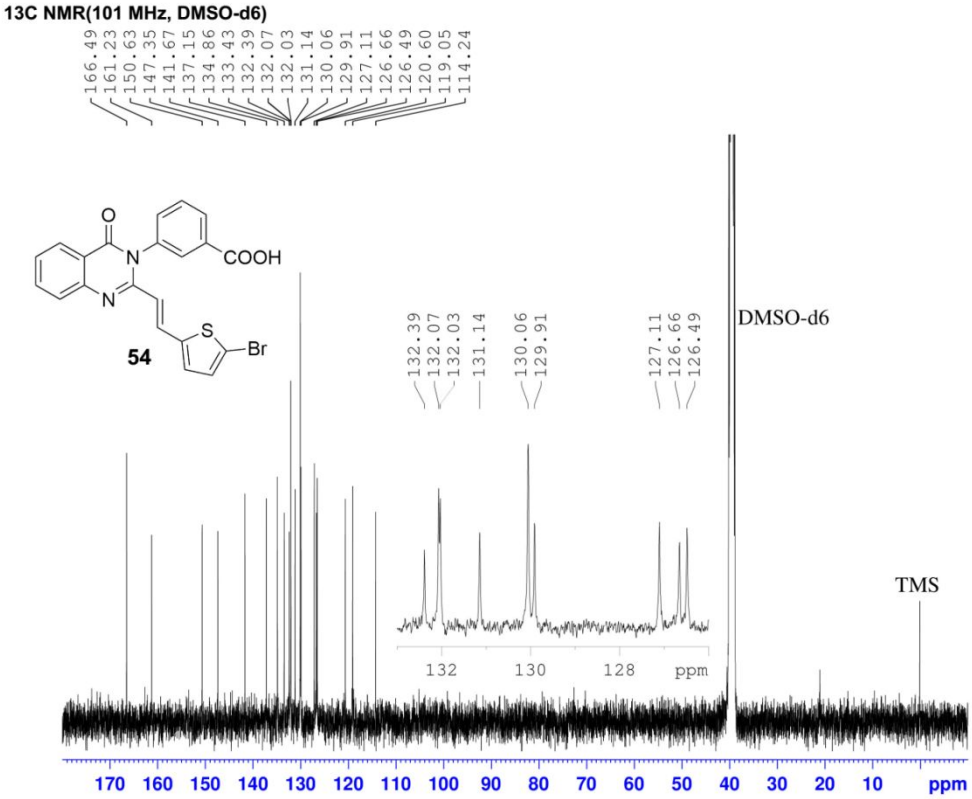


(*E*)-2-(2-(5-Bromothiophen-2-yl)vinyl)-3-(3-carboxyphenyl)quinazolin-4(3*H*)-one (54).

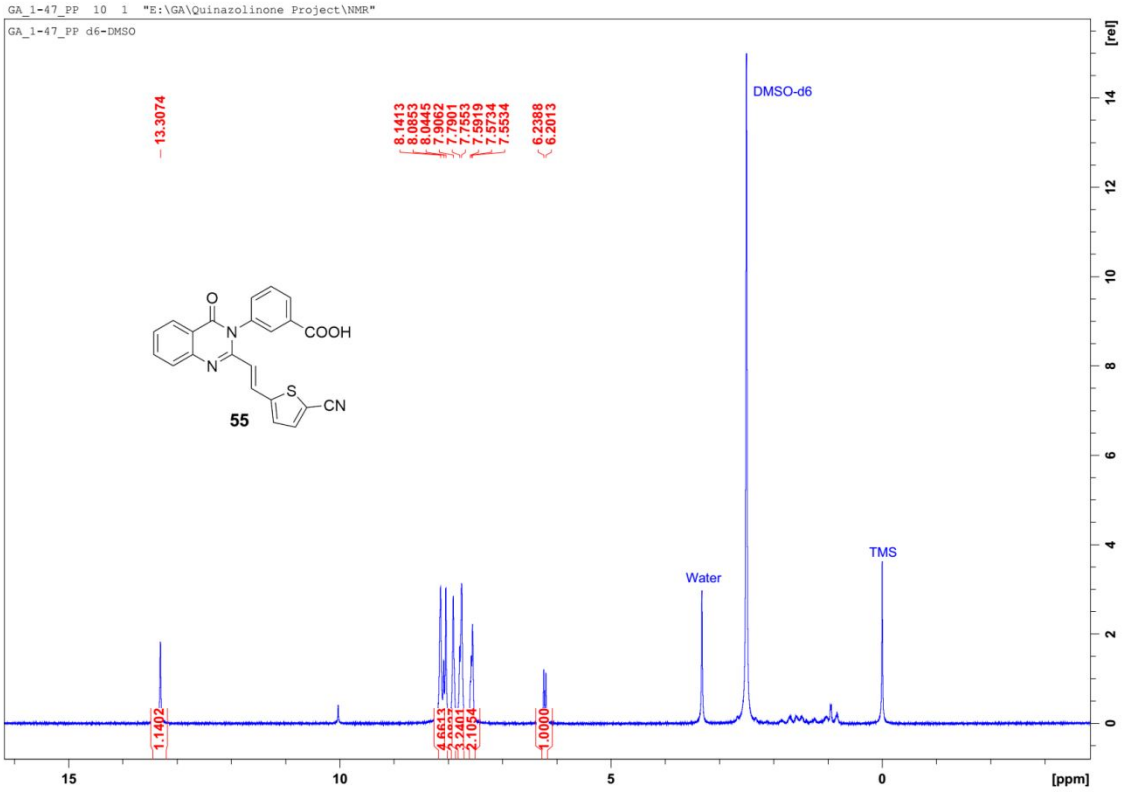
1H NMR （400 MHz, DMSO-d6)

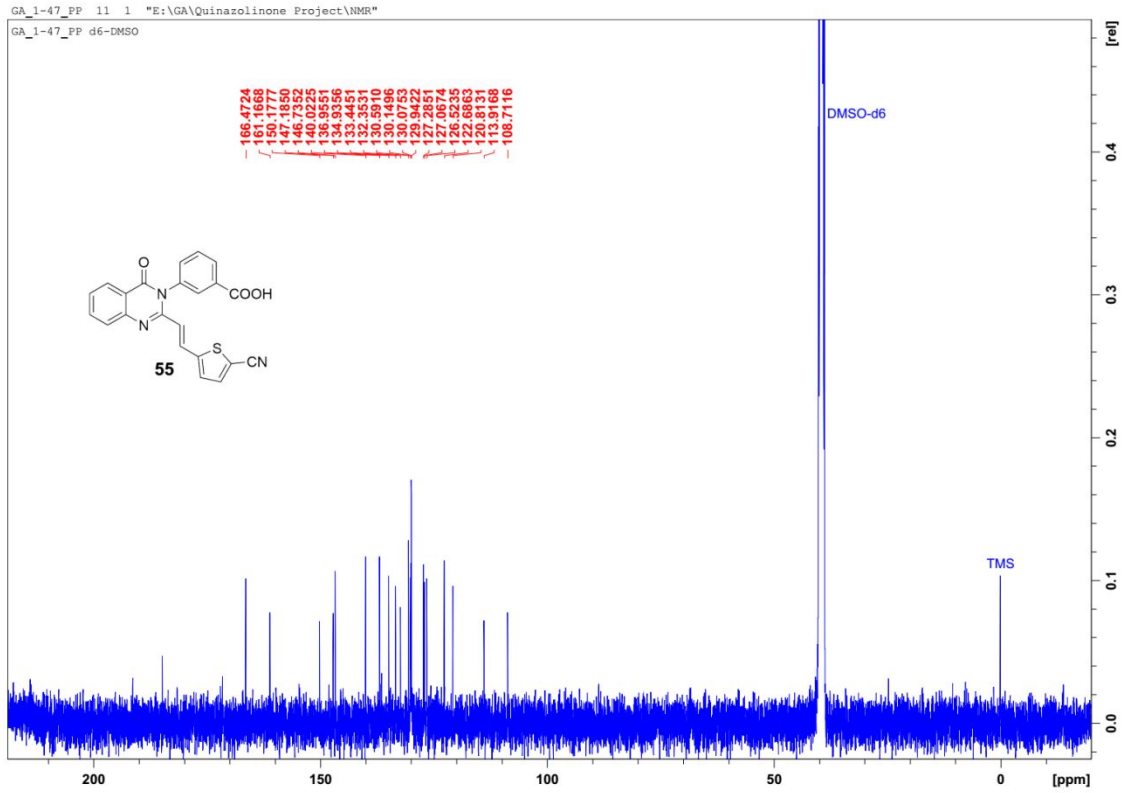


13C NMR(101 MHz, DMSO-d6)

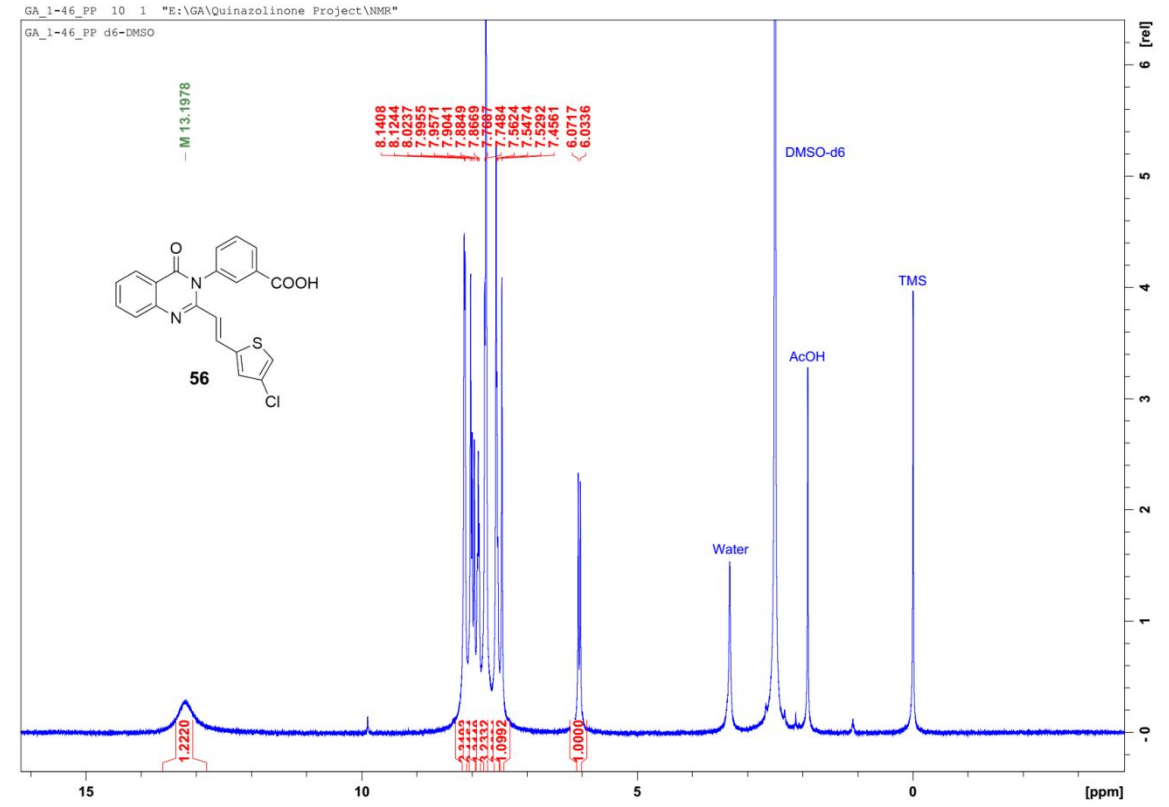


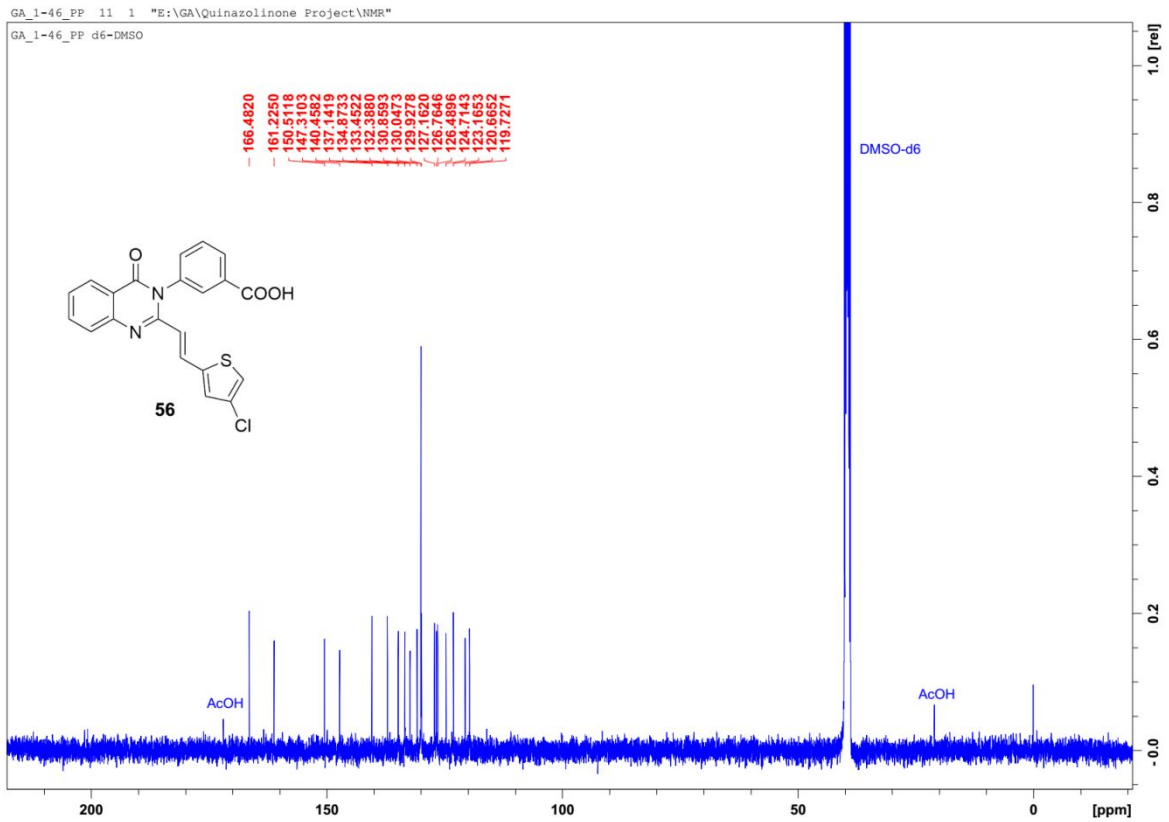
(*E*)-3-(3-Carboxyphenyl)-2-(2-(5-cyanophen-2-yl)vinyl)quinazolin-4(3*H*)-one (55).



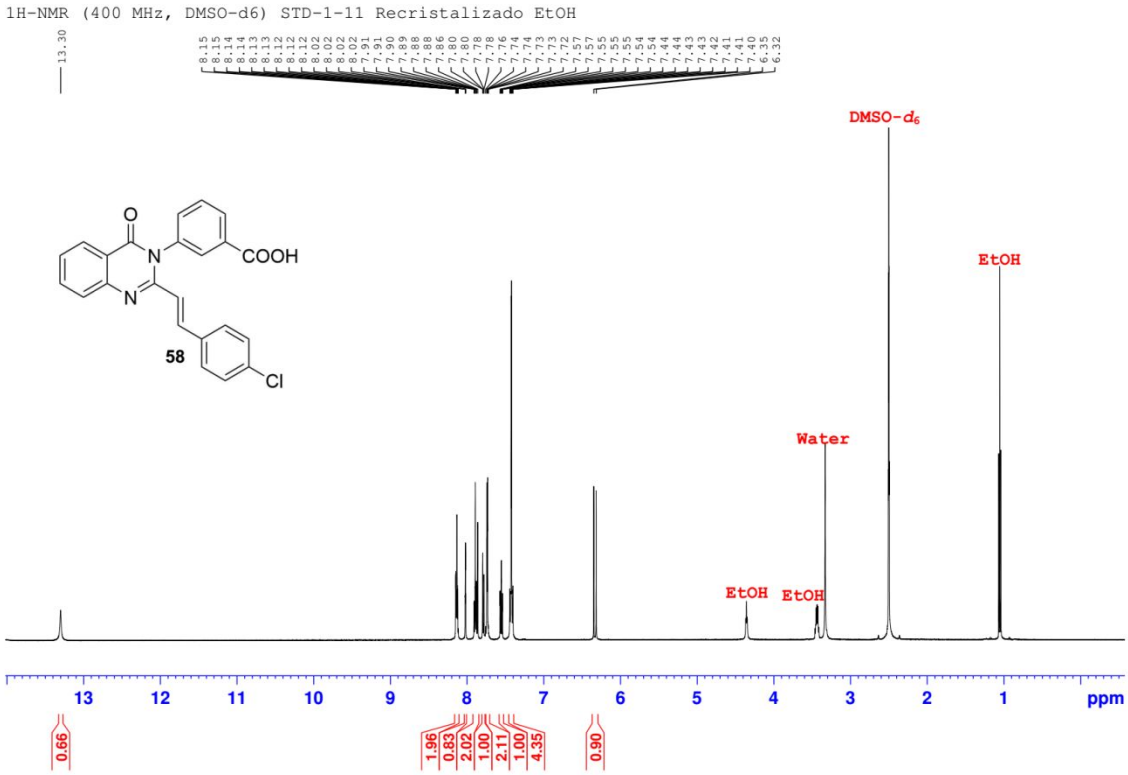


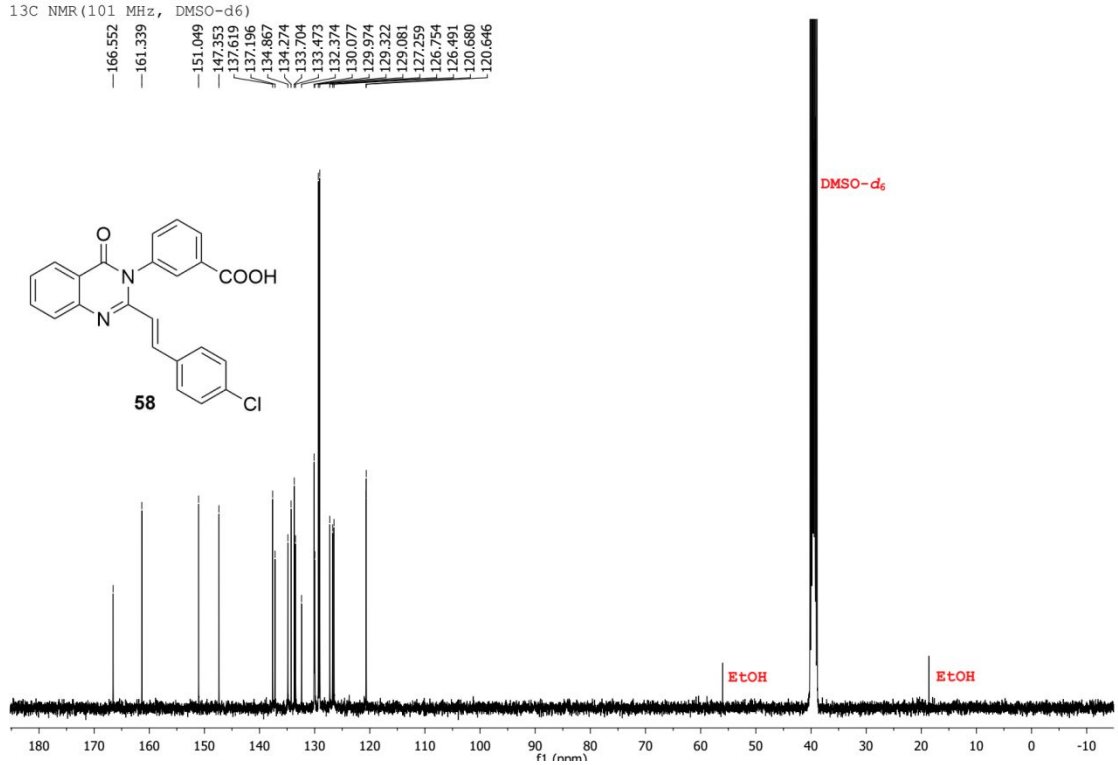
(*E*)-3-(3-Carboxyphenyl)-2-(2-(4-chlorothiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (56).



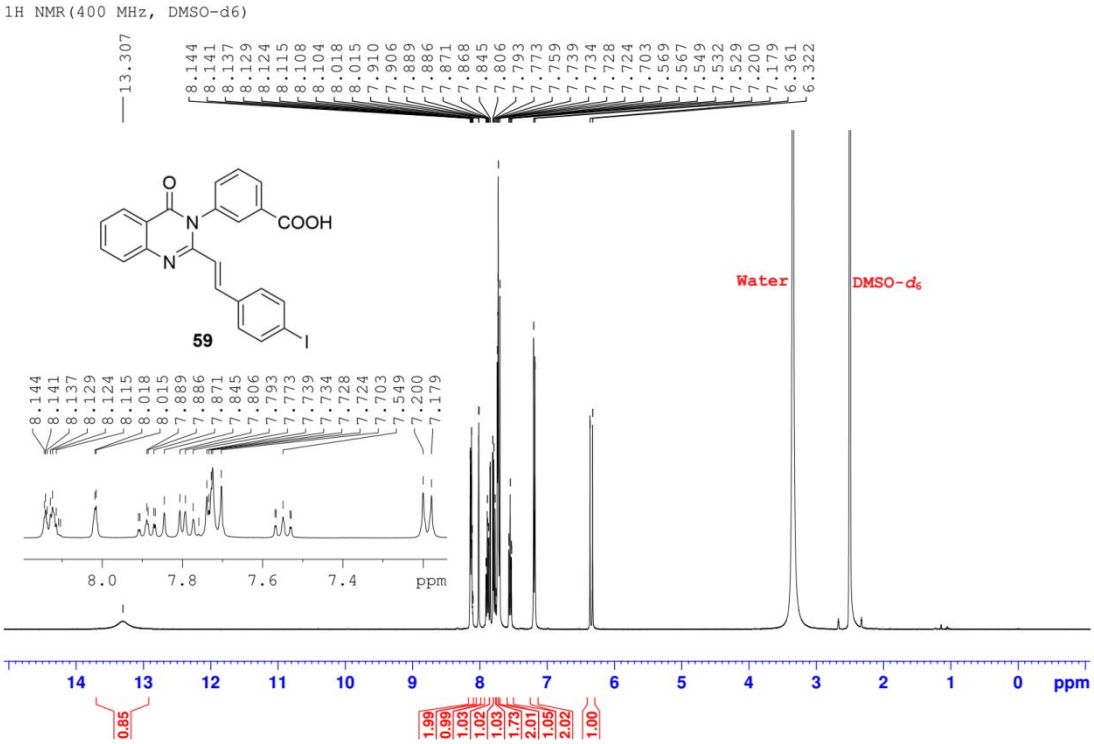


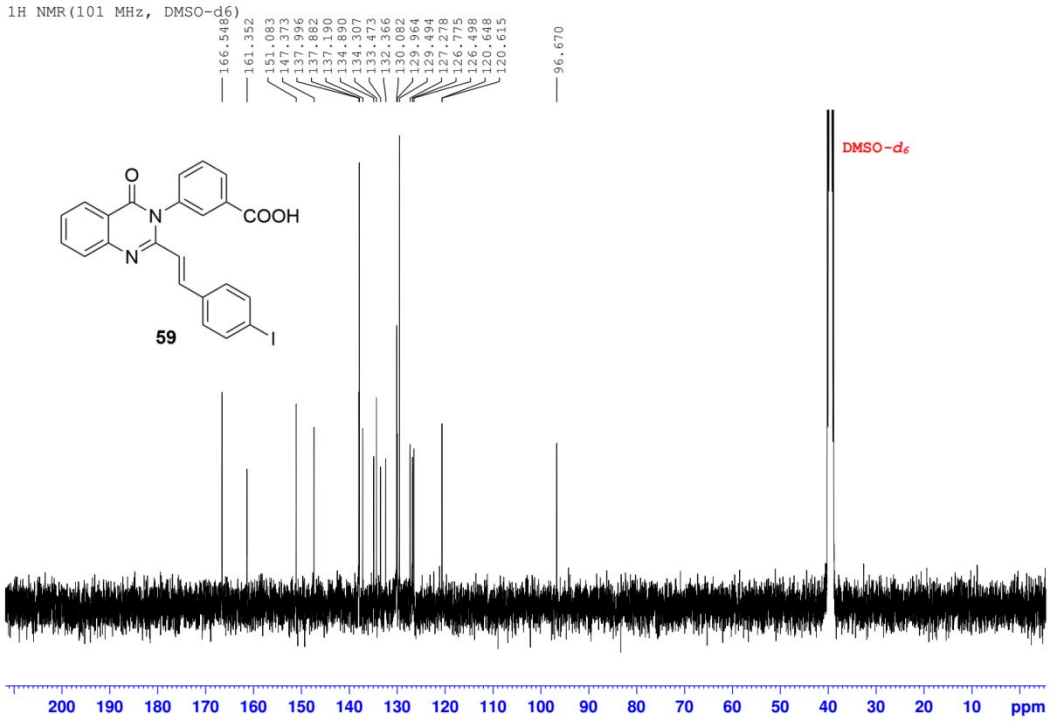
(*E*)-3-(3-Carboxyphenyl)-2-(4-chlorostyryl)quinazolin-4(3*H*)-one (58).



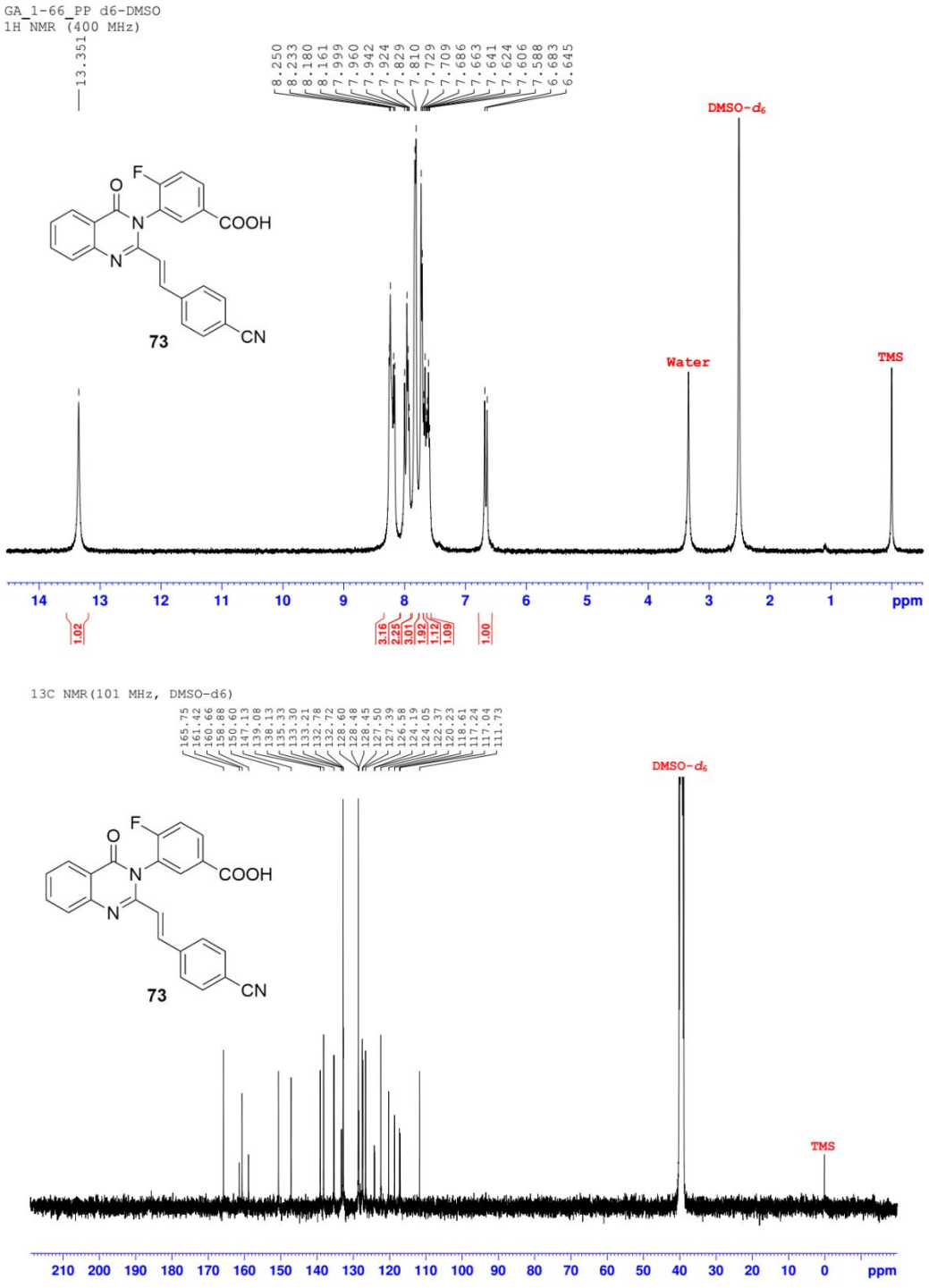


(*E*)-3-(3-Carboxyphenyl)-2-(4-iodostyryl)quinazolin-4(3*H*)-one (59).

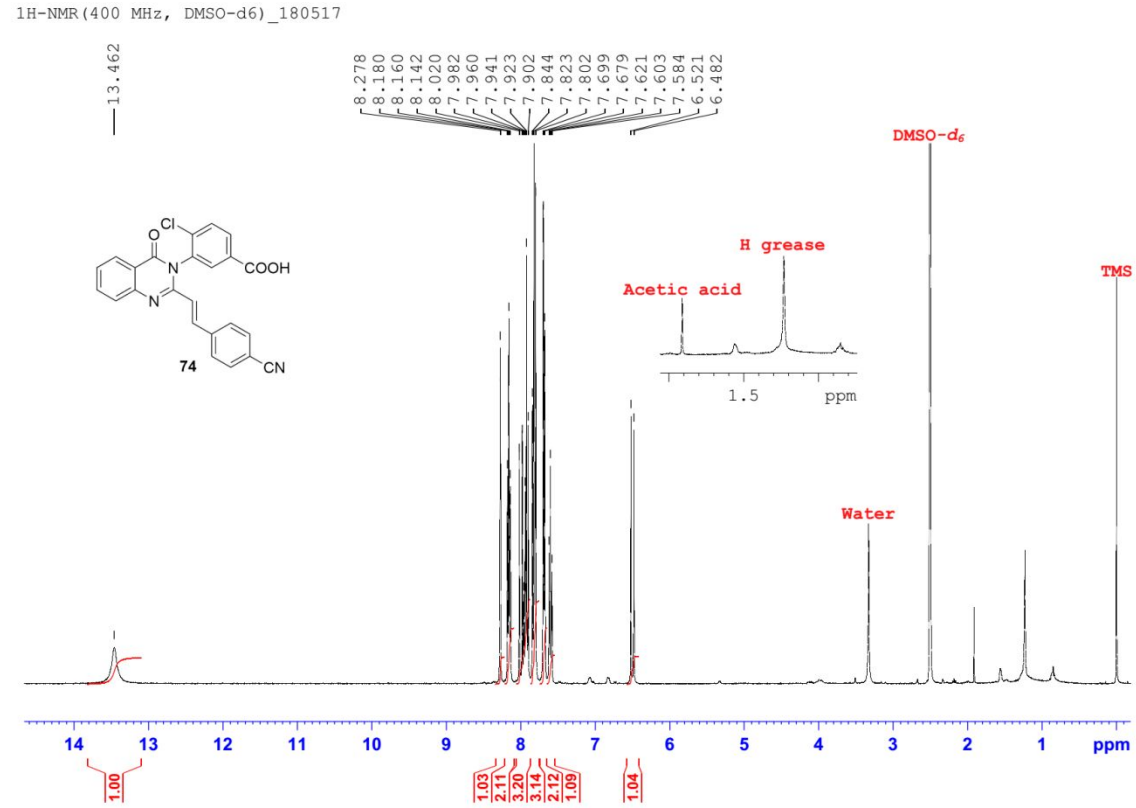


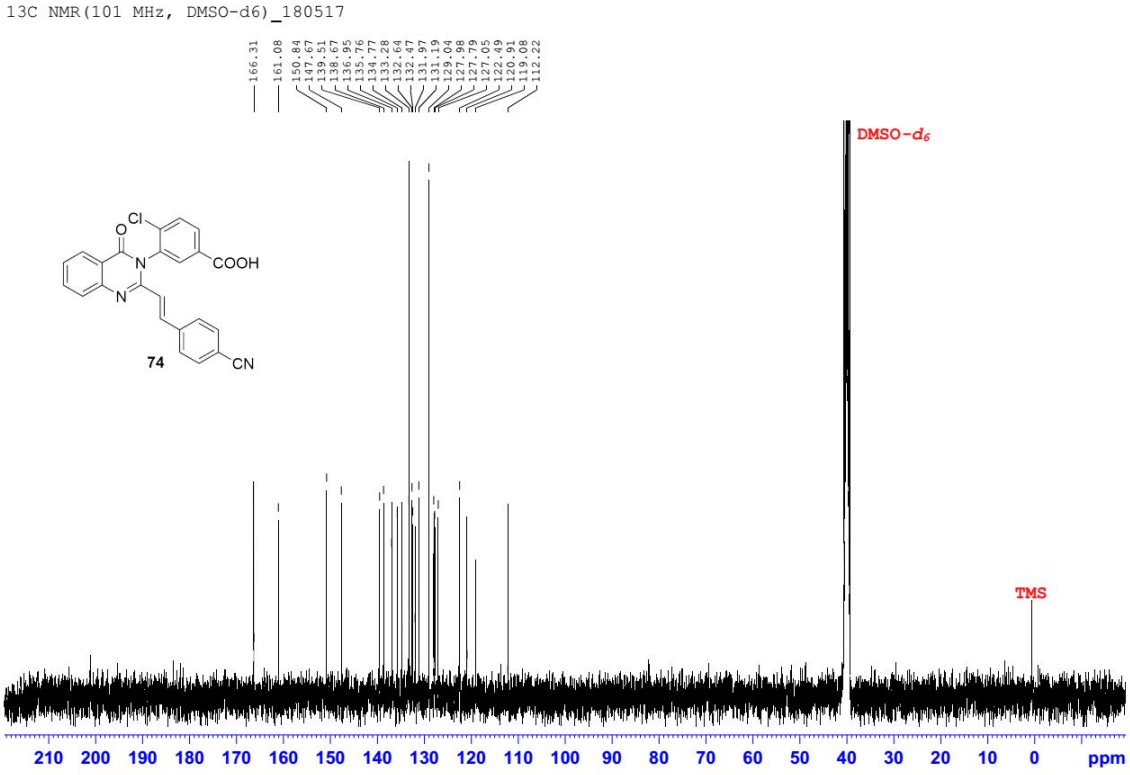


(*E*)-3-(5-Carboxy-2-fluorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (73).

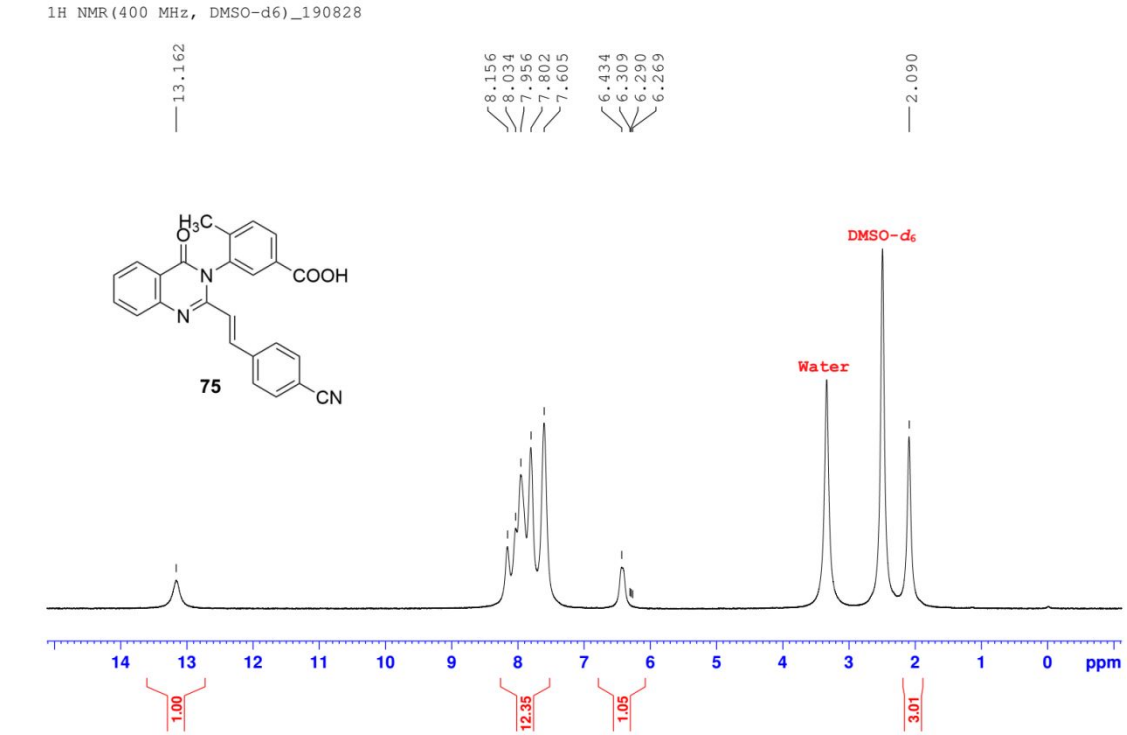


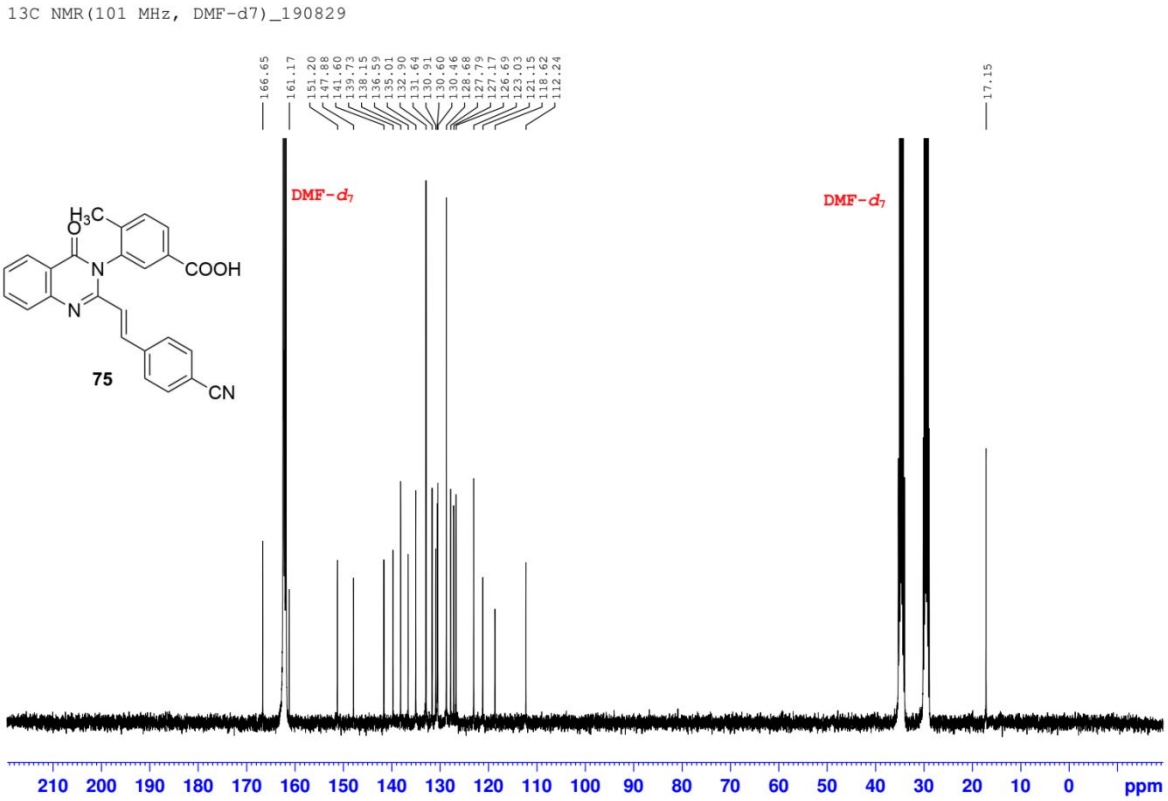
(*E*)-3-(5-Carboxy-2-chlorophenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (74).



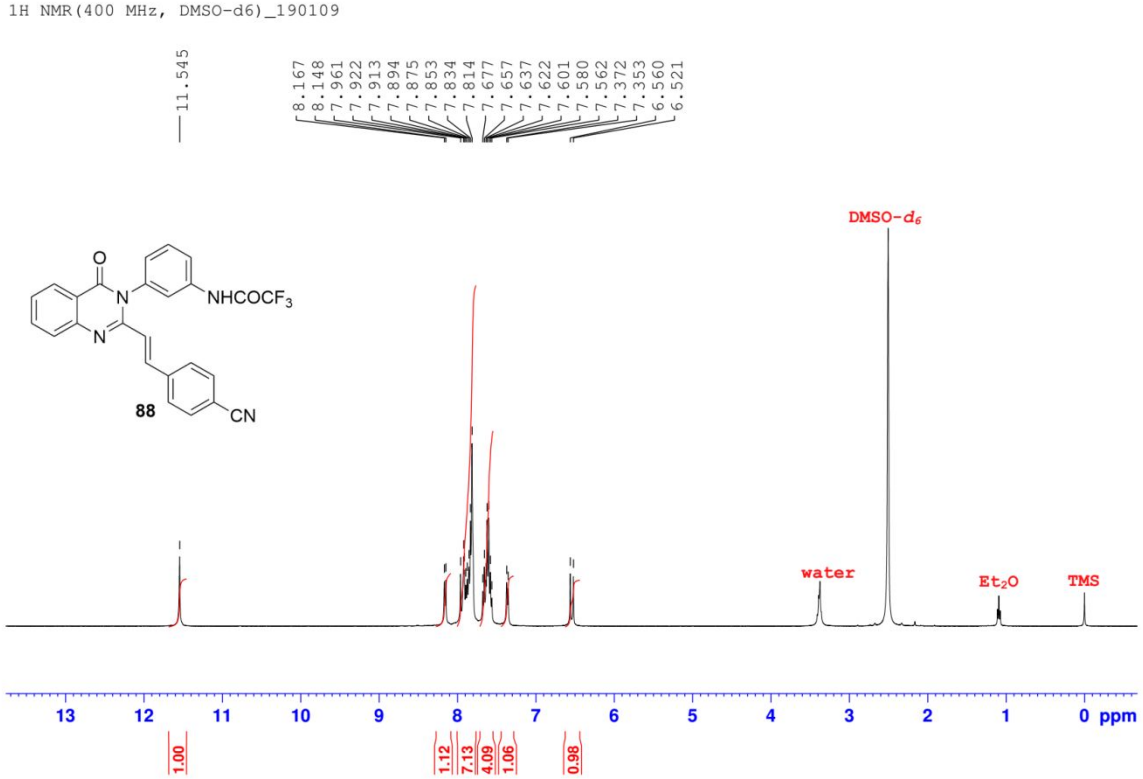


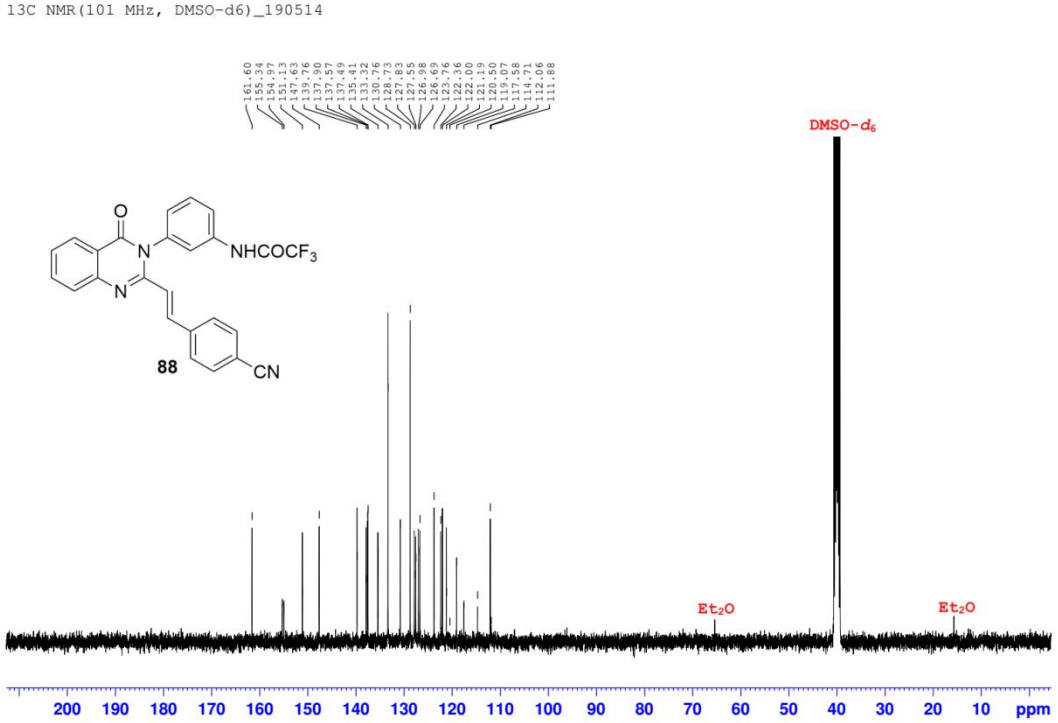
(*E*)-3-(3-Carboxy-6-methylphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (75).



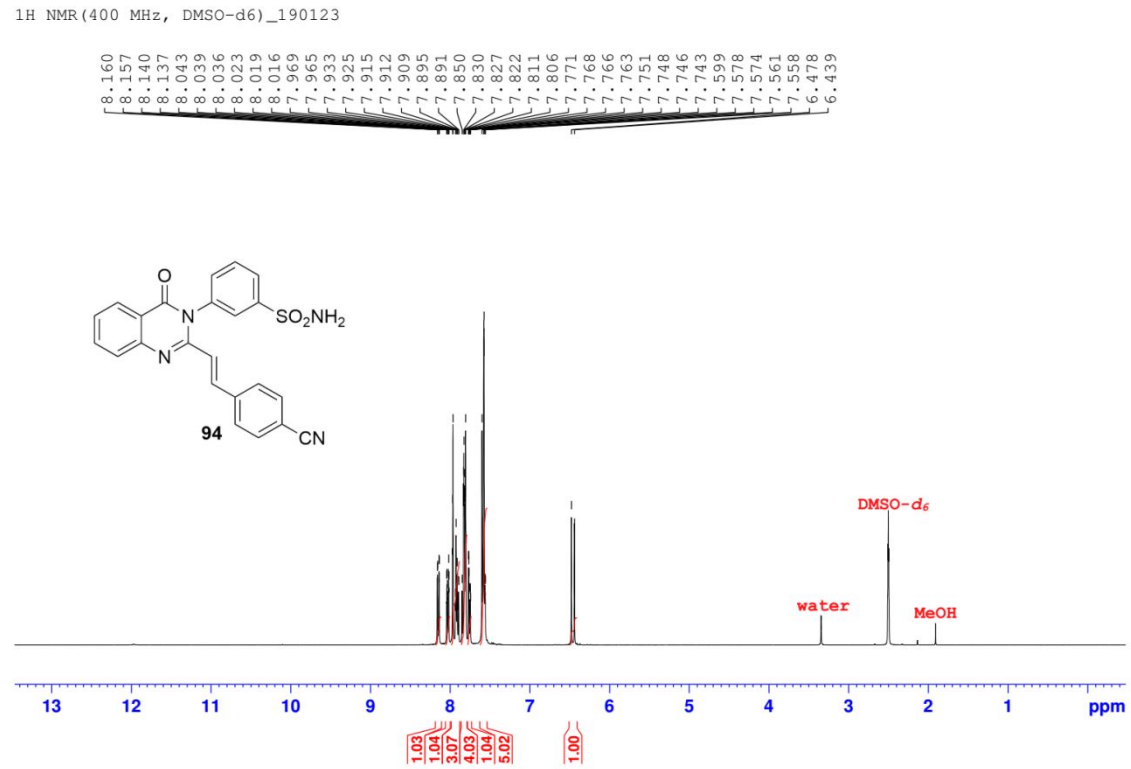


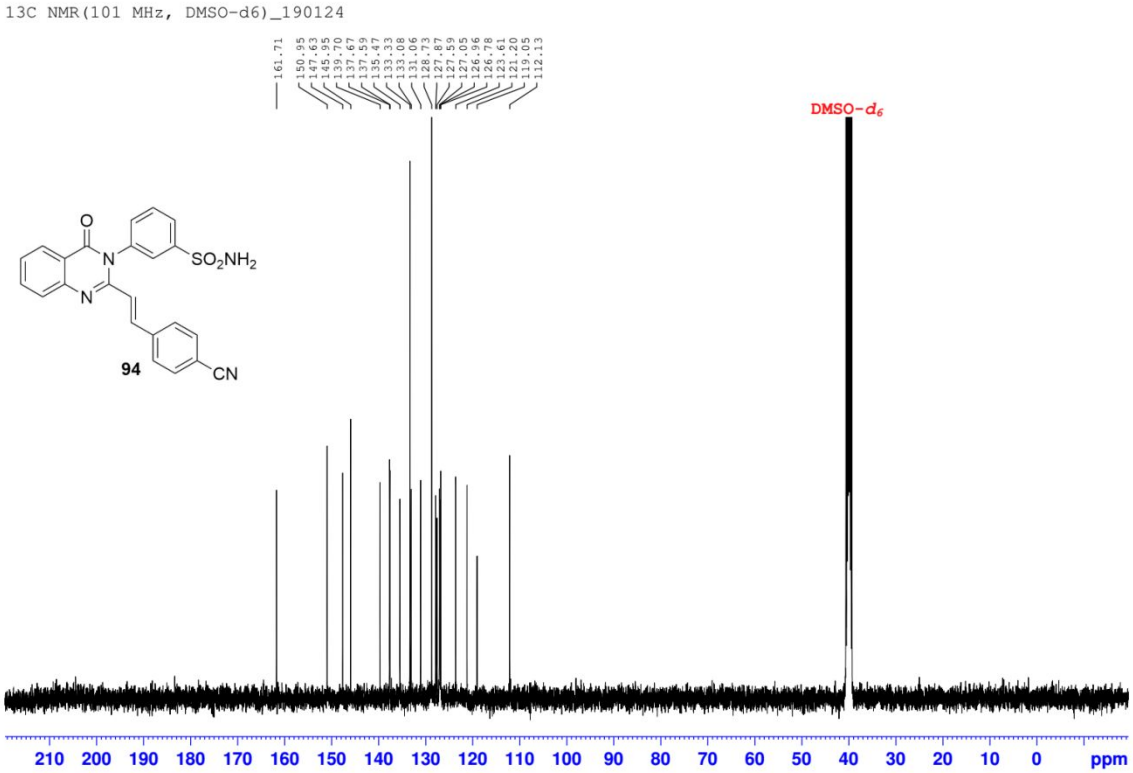
(E)-N-(3-(2-(4-cyanostyryl)-4-oxoquinazolin-3(4*H*)-yl)phenyl)-2,2,2-trifluoroacetamide (88)



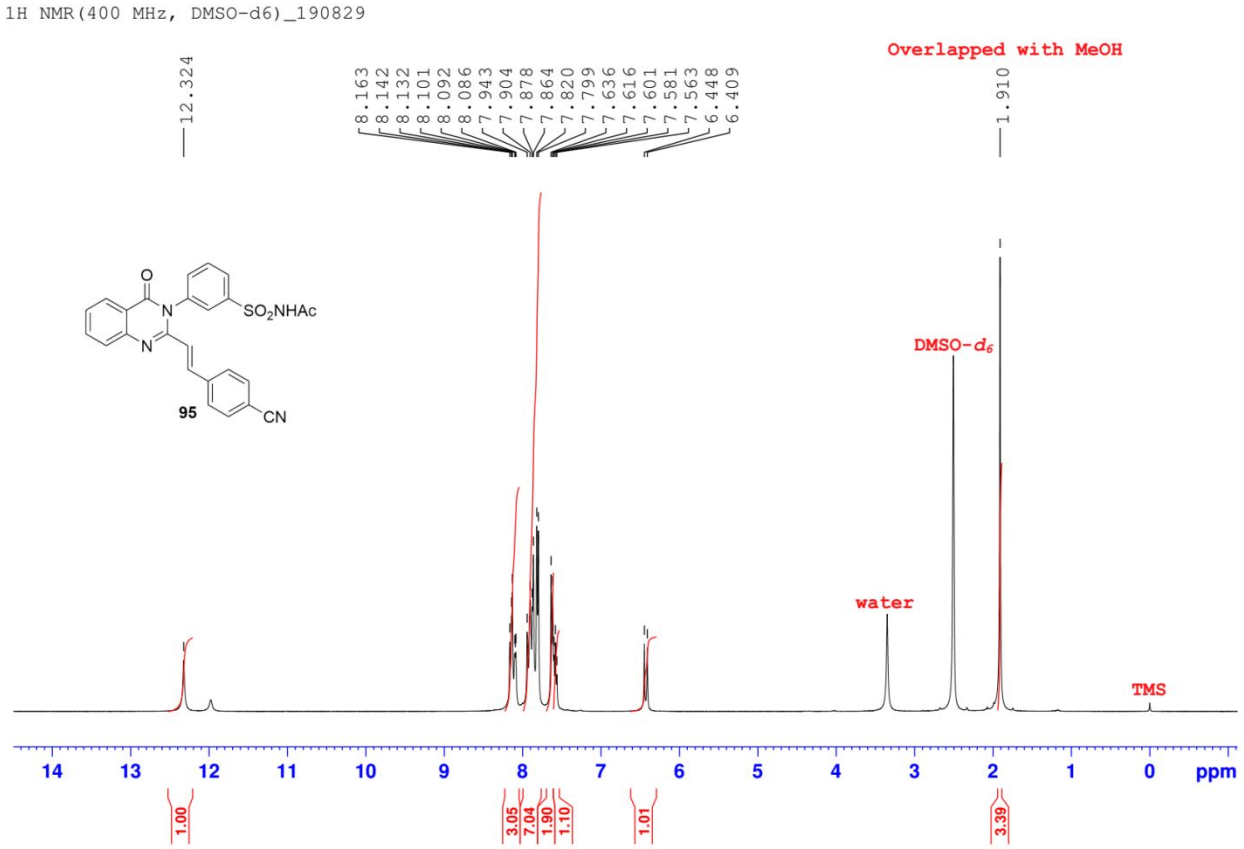


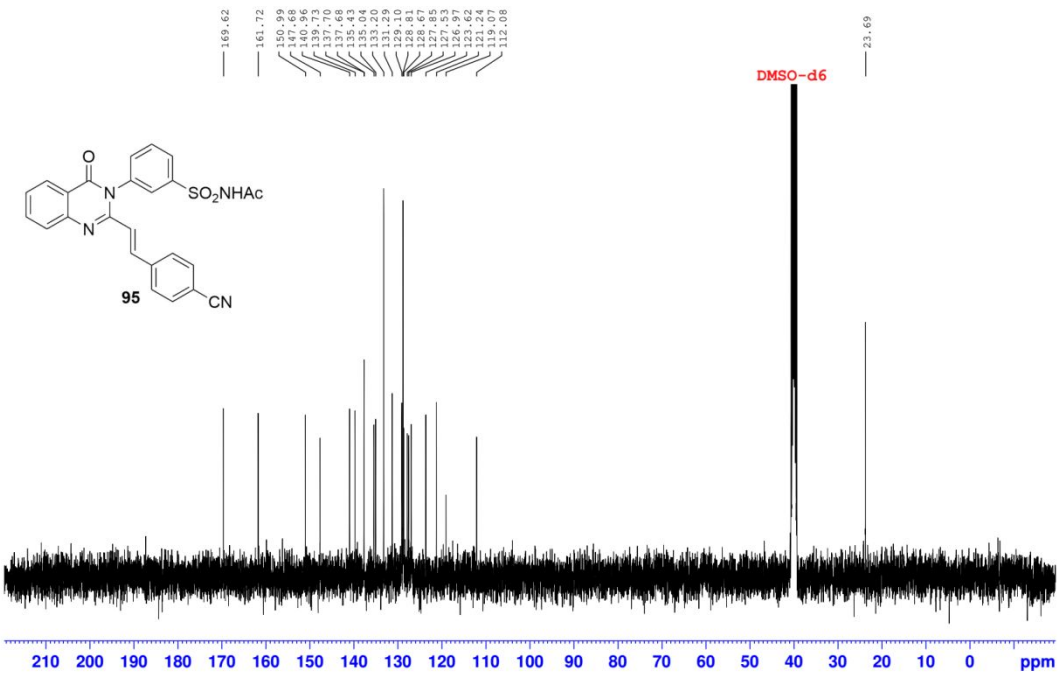
(*E*)-2-(4-Cyanostyryl)-3-(3-sulfamoylphenyl)quinazolin-4(3*H*)-one (94).



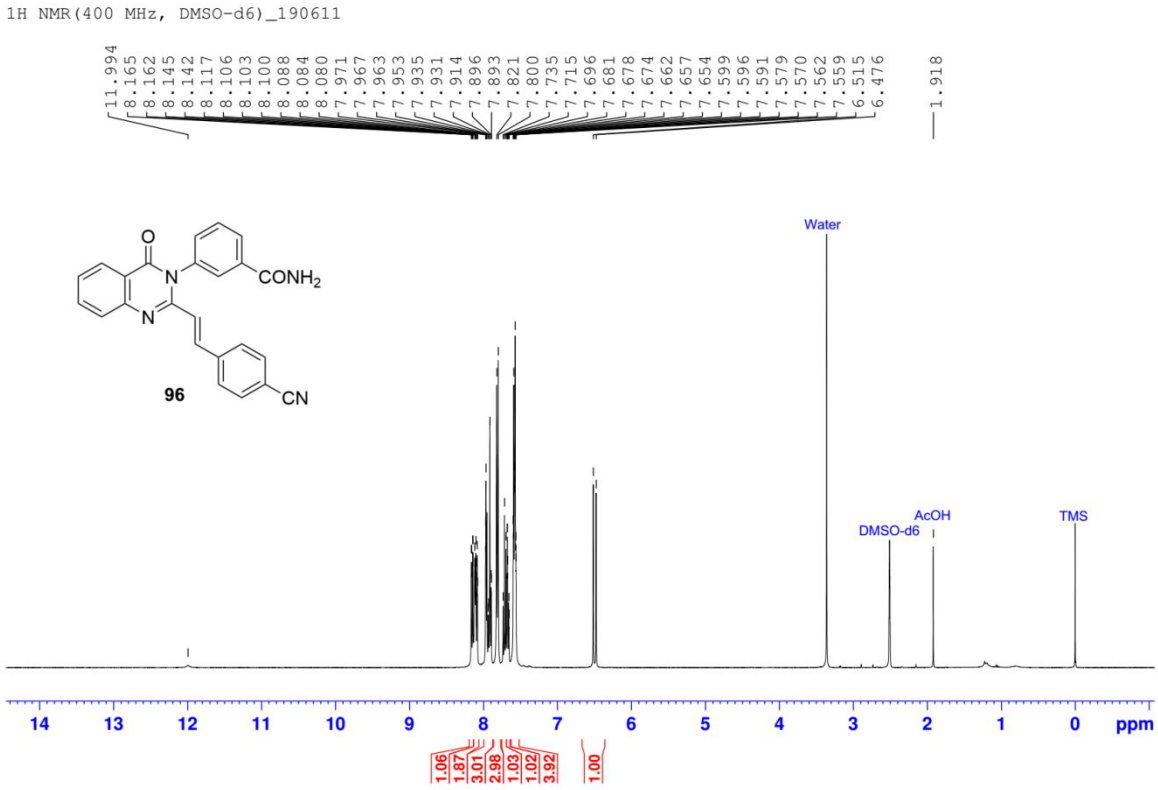


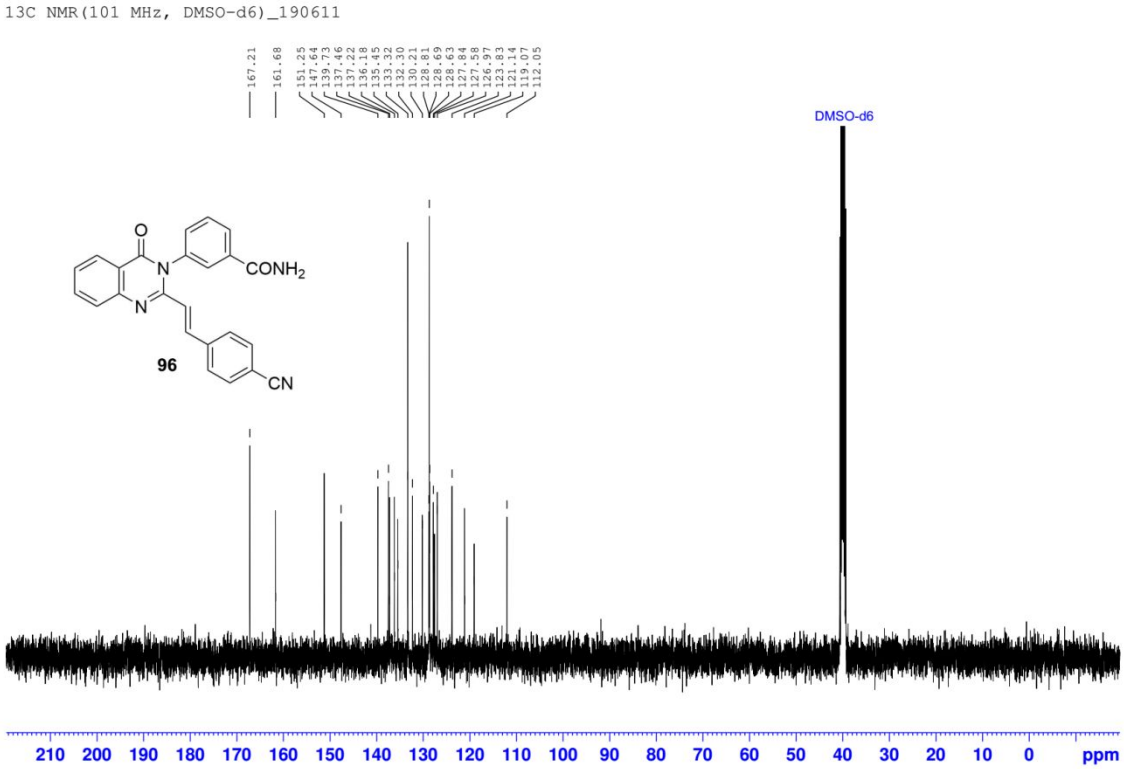
(*E*)-2-(4-Cyanostyryl)-3-(3-(*N*-acetylsulfamoyl)phenyl)quinazolin-4(3*H*)-one (95).



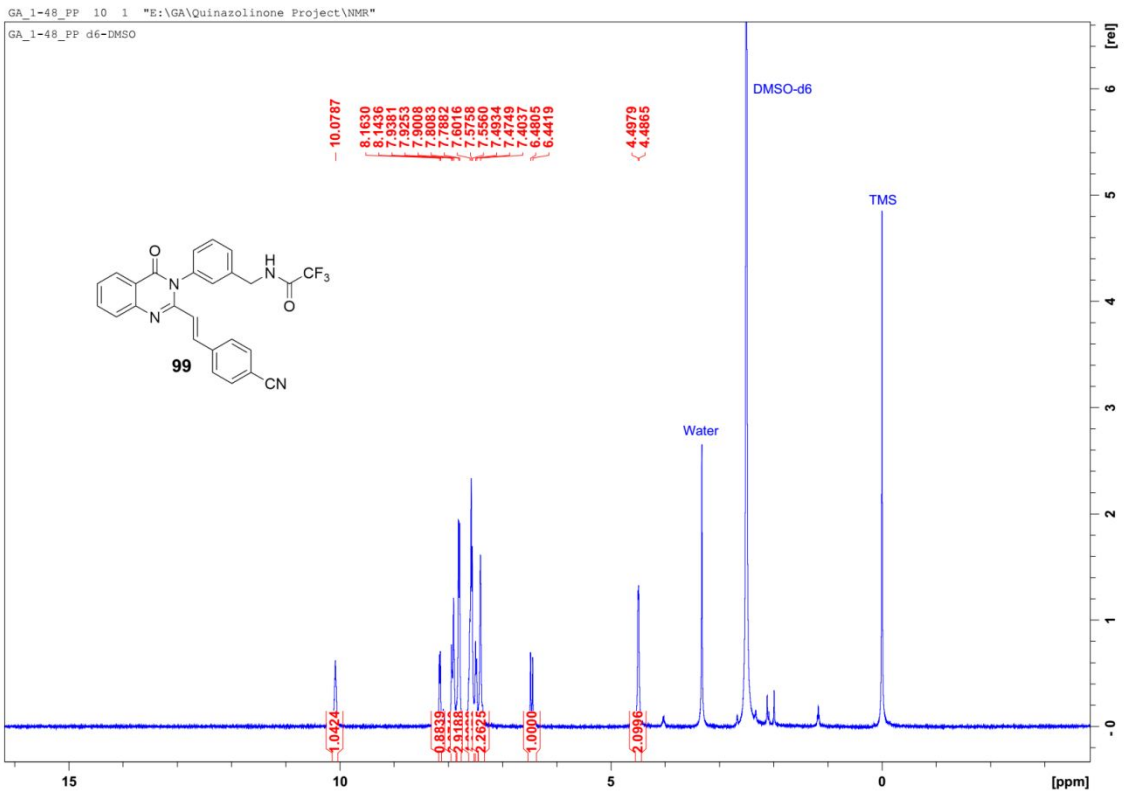


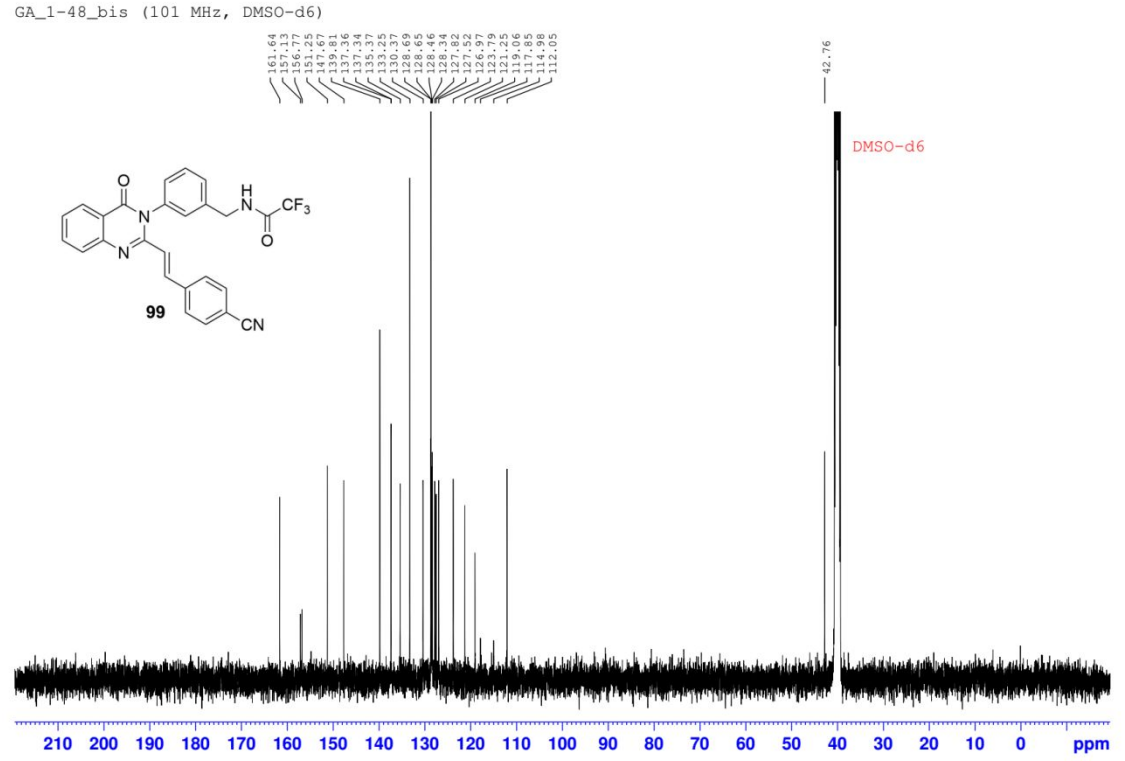
(*E*)-3-(3-Carbamoylphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one (96).



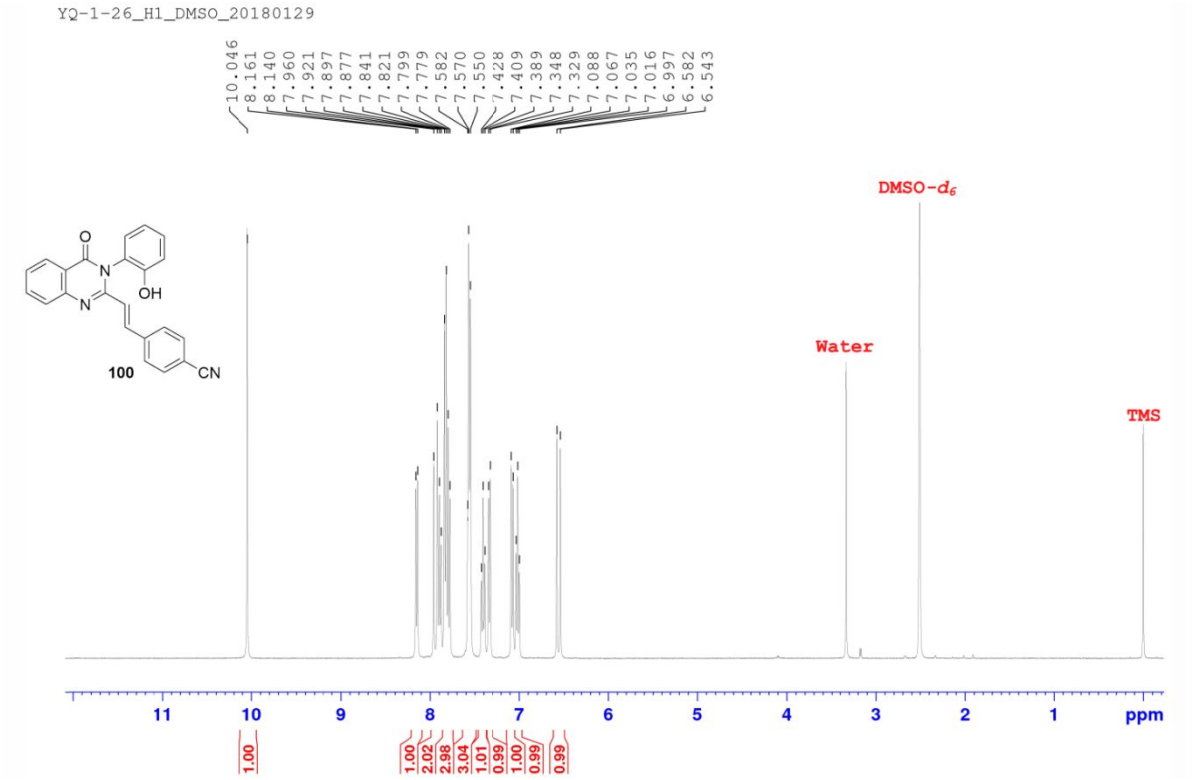


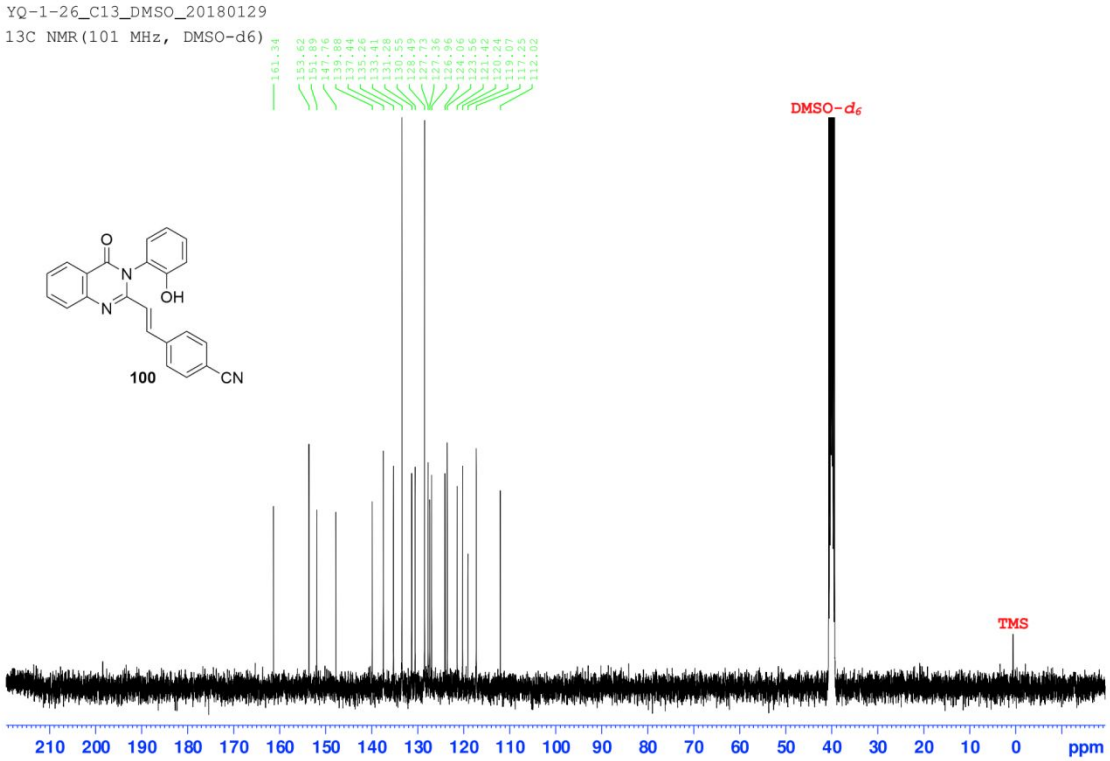
(*E*)-2-(4-Cyanostyryl)-3-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)quinazolin-4(3*H*)-one (99).



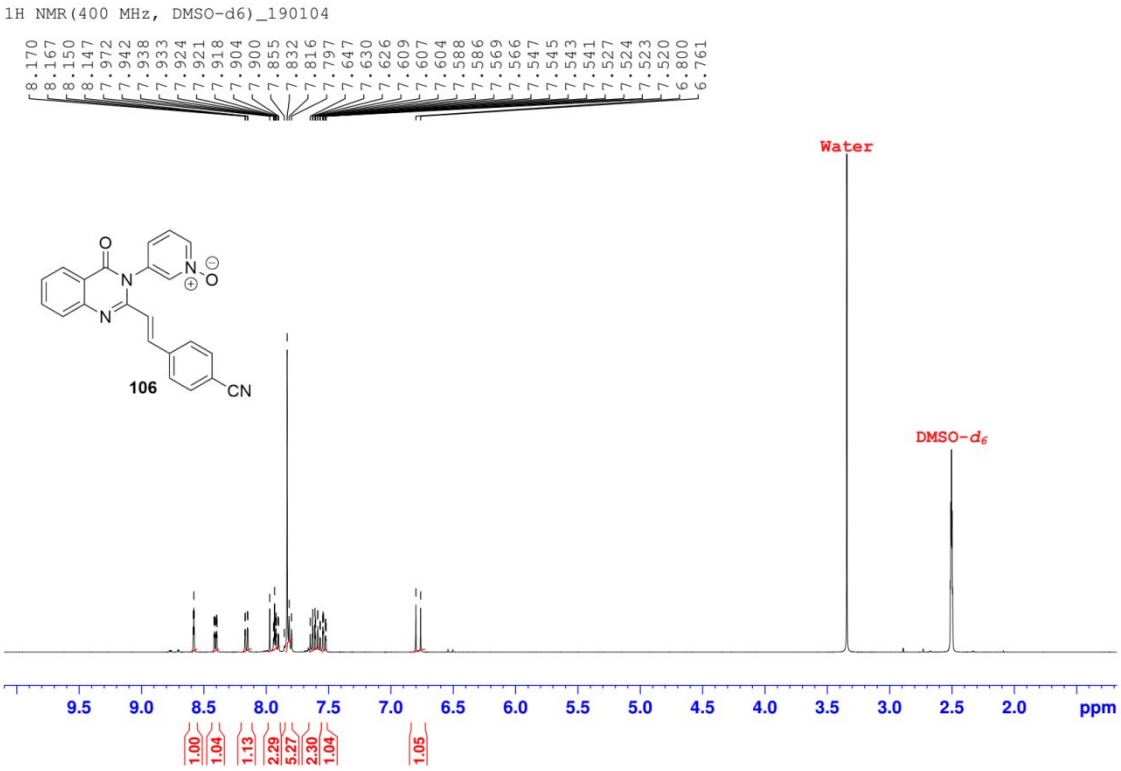


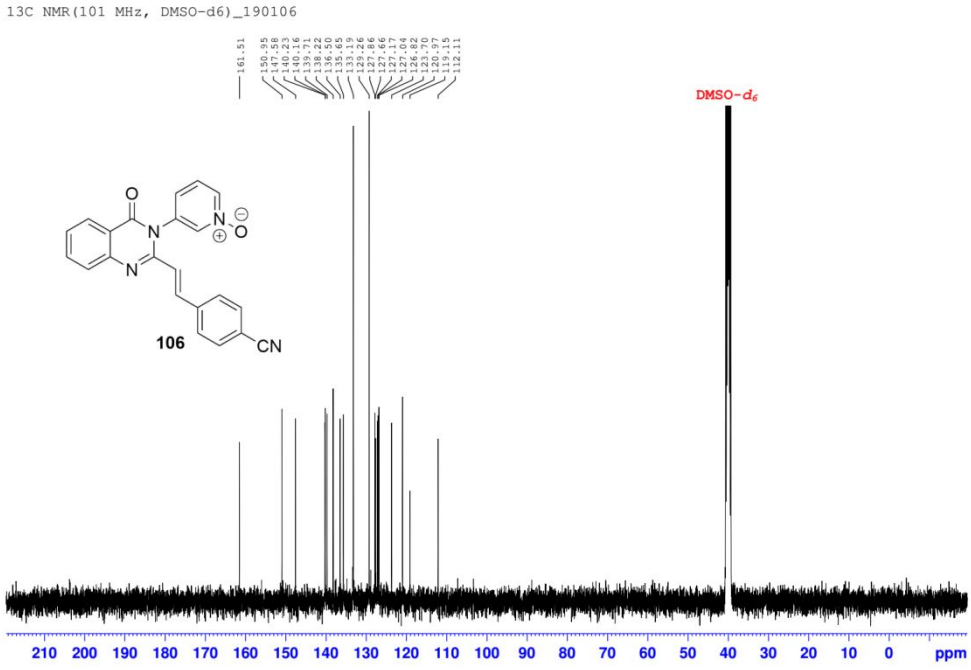
(*E*)-2-(4-Cyanostyryl)-3-(2-hydroxyphenyl)quinazolin-4(3*H*)-one (100).



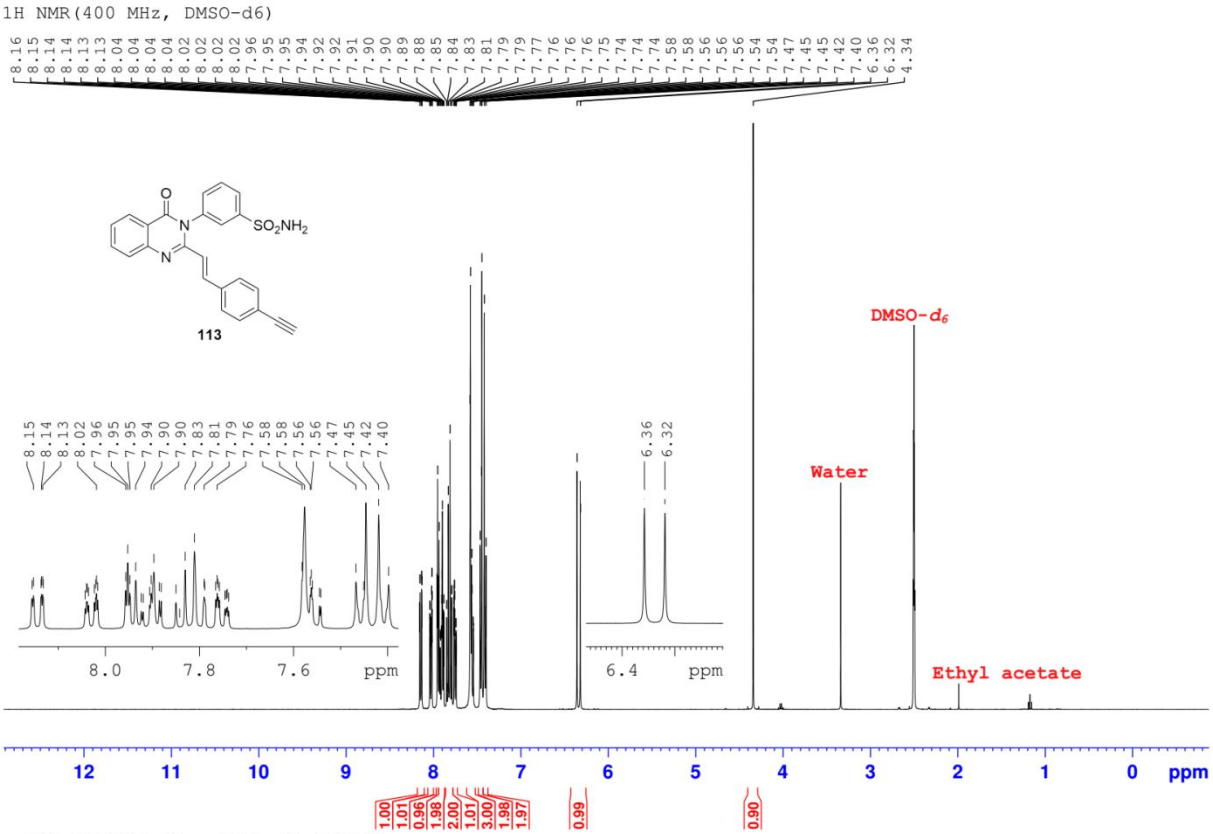


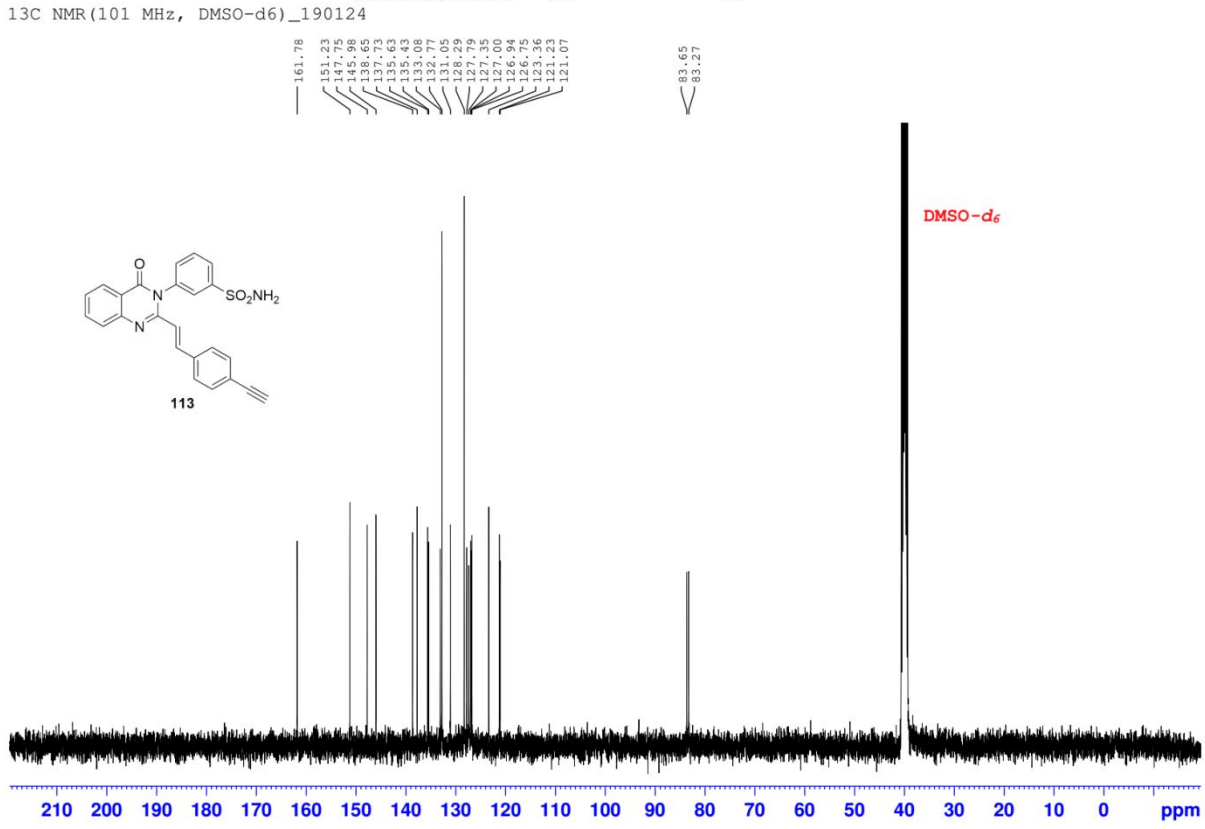
(*E*)-2-(4-Cyanostyryl)-3-(1-oxidopyridin-3-yl)quinazolin-4(3*H*)-one (106).



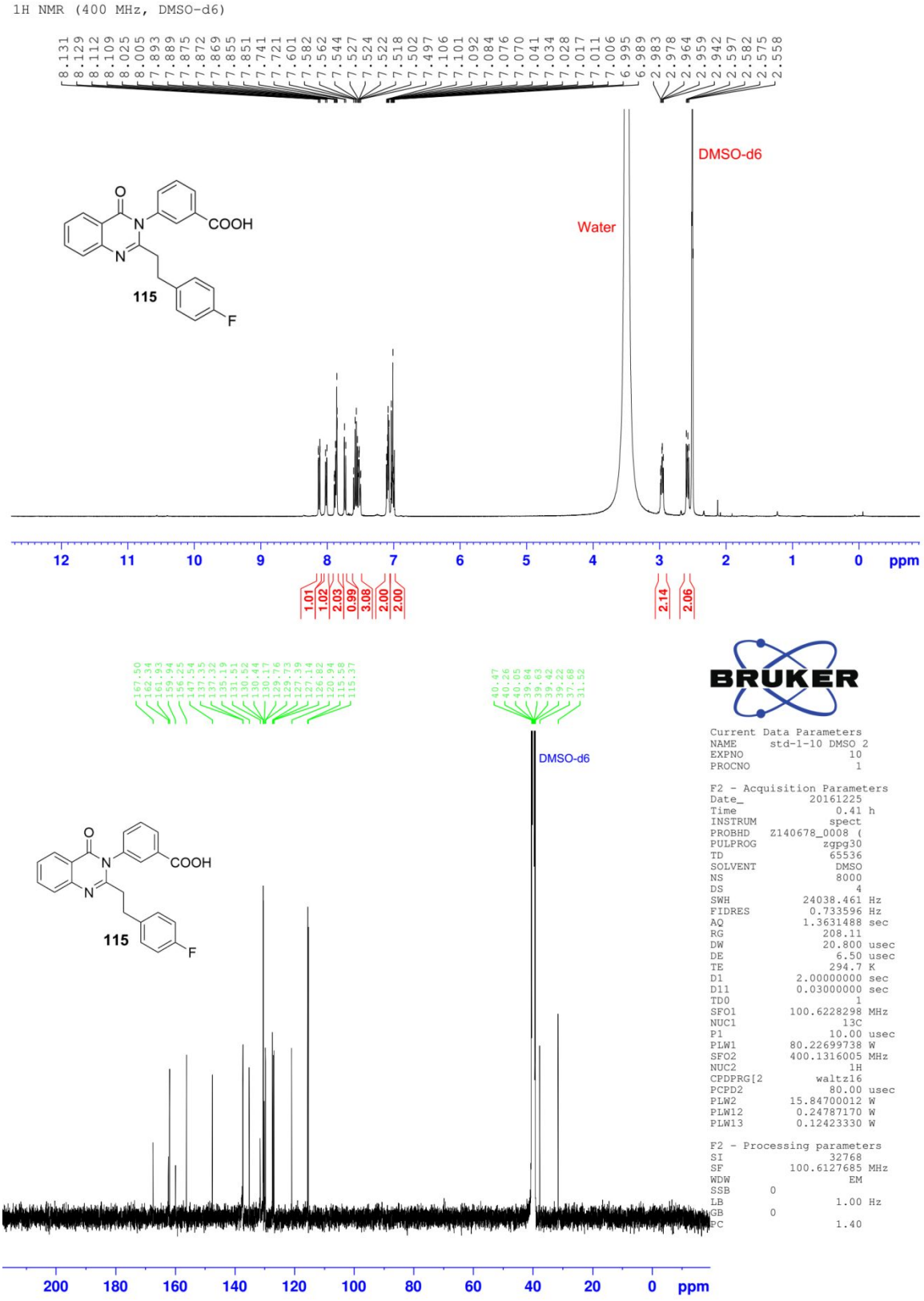


(*E*)-2-(4-Ethynylstyryl)-3-(3-sulfamoylphenyl)quinazolin-4(3*H*)-one (113).

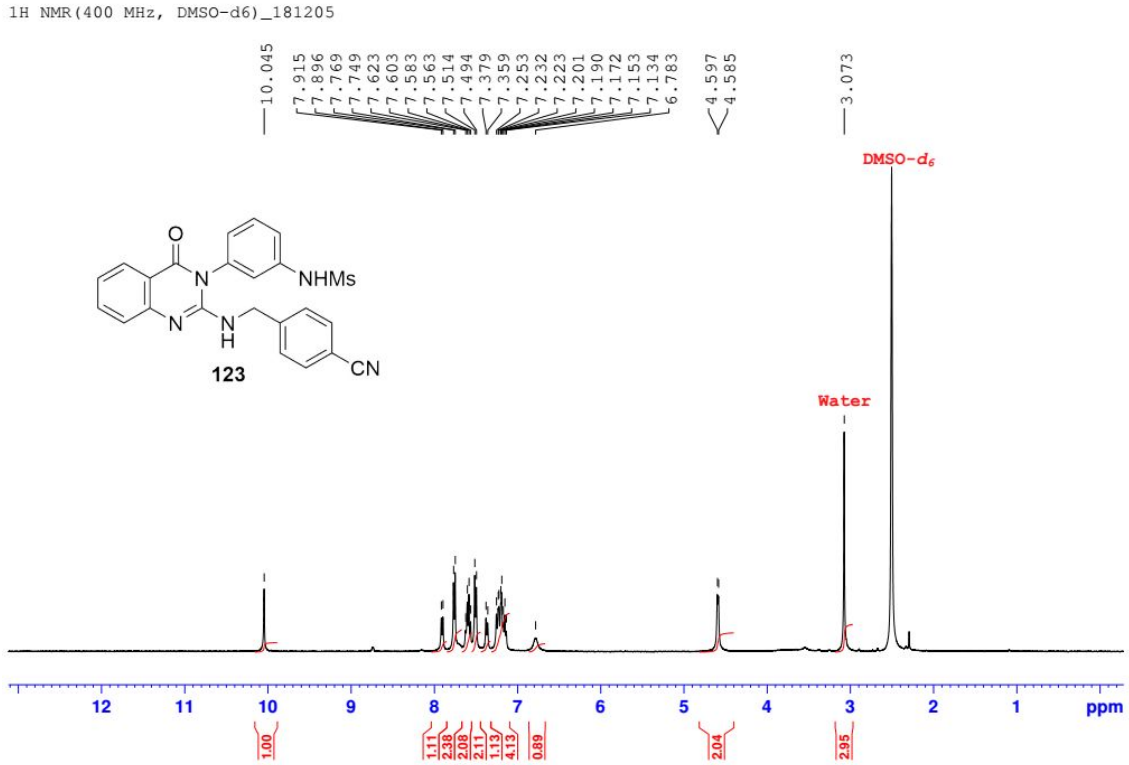


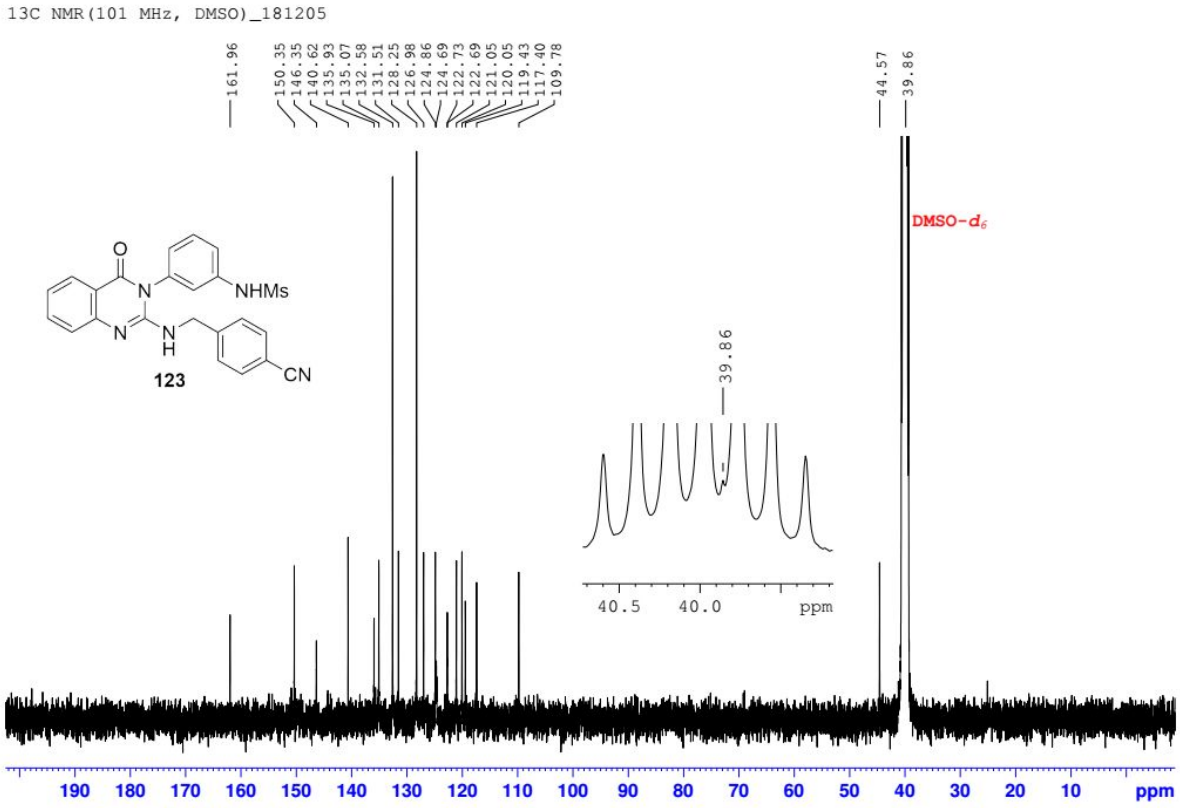


(*E*)-3-(3-Carboxyphenyl)-2-(4-fluorophenethyl)quinazolin-4(3*H*)-one (115).

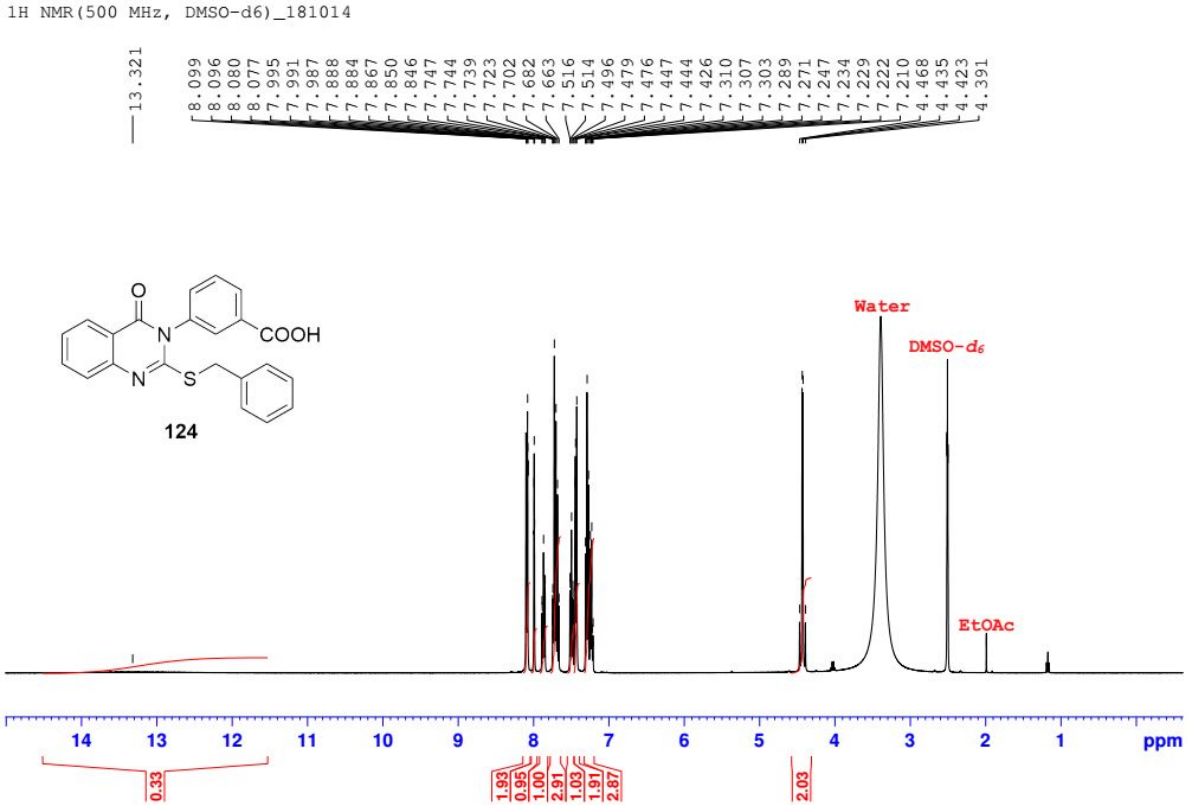


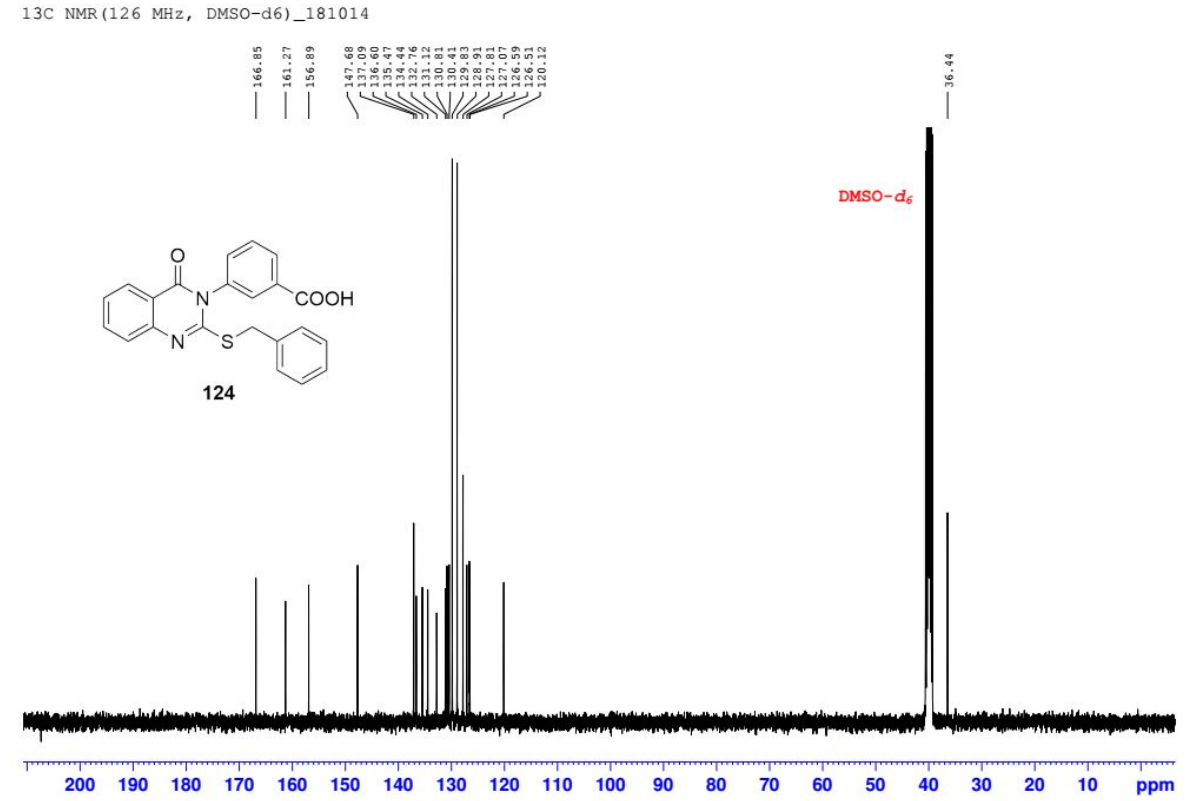
(*E*)-2-((4-Cyanobenzyl)amino)-3-(3-methylsulfonamidophenyl)quinazolin-4(3*H*)-one (123).



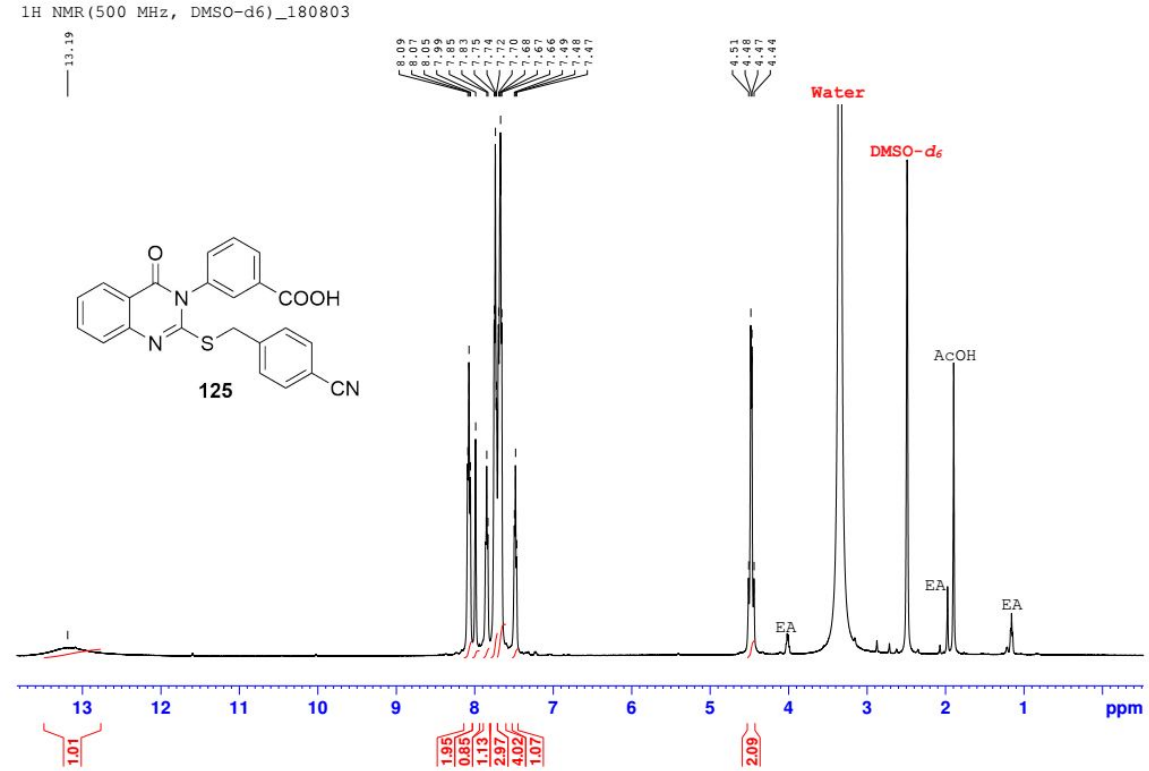

13C NMR(101 MHz, DMSO)_181205
161.96
150.35
146.35
140.62
135.93
135.07
132.58
131.51
128.25
126.98
124.86
124.69
122.73
122.69
121.05
120.05
119.43
117.40
109.78
44.57
39.86
DMSO-d_6
NHMs
CN
123
39.86
40.5
40.0
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

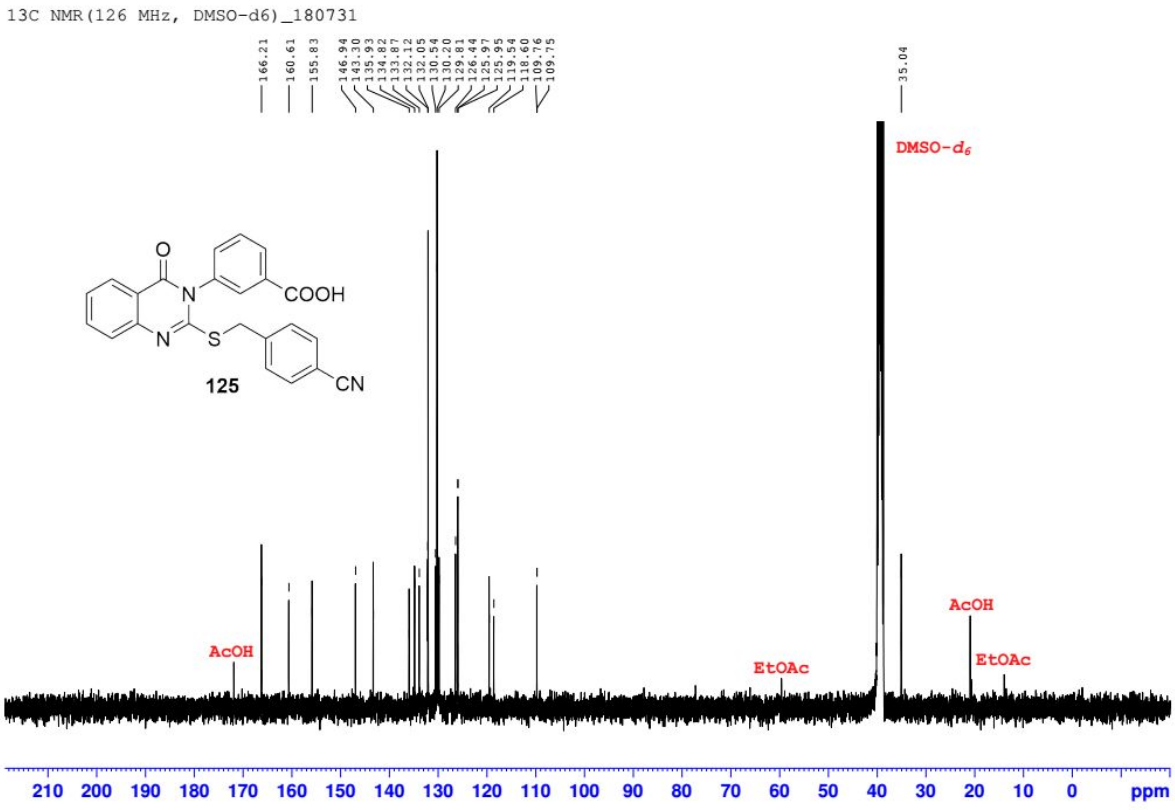
(*E*)-2-(Benzylthio)-3-(3-carboxyphenyl)quinazolin-4(3*H*)-one (124).





(*E*)-3-(3-Carboxyphenyl)-2-((4-cyanophenyl)thio)quinazolin-4(3*H*)-one (125).





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