**Supporting information**

**Synthesis and Biological Applications of Some Novel 8-Hydroxyquinoline Urea and Thiourea Derivatives**

1. *Chemistry*
   1. *Synthesis of 5-piperazineomethyl-8-hydroxyquinoline.3HCl (2)*

To a solution of 0.45 g of 5-(N’-Boc-piperazineomethyl)-8-hydroxyquinoline in 15 mL of dry dioxane, was added 3mL of 4M HCl in dioxane. The mixture was stirred for 2 hours at 25°C then dried under vacuum to give the product as yellow powder in quantitative yield. 1H NMR (400 MHz, D2O) δ 9.26 (dd, *J* = 8.8, 1.3 Hz, 1H), 8.96 (dd, *J* = 5.5, 1.3 Hz, 1H), 8.06 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.84 (d, *J* = 1.2 Hz, 2H), 3.50 (ddd, *J* = 49.2, 7.1, 3.7 Hz, 8H). 13C NMR (101 MHz, D2O) δ 149.7, 143.1, 143.1, 143.0, 136.5, 129.8, 129.3, 123.0, 115.6, 115.6, 115.5, 66.5, 55.9, 48.2, 40.7.

* 1. *General synthesis of 8-hydroxyquinoline-carbothioamide (5a-h) and 8-hydroxyquinoline carboxamide derivatives (6b-d)*

To a stirred solution of 5-piperazineomethyl-8-hydroxyquinoline **2** (0.55 mmol) in dry acetonitrile (10 mL), was added excess triethylamine (4.5 mmol) and the corresponding isothiocyanatobenzene **3a-h** or isocyanatobenzene **4b-d** (0.5 mmol). The mixture was stirred at room temperature for 1.5- 2h and the solvent was removed under vacuum. The residue was extracted by addition of water (20 mL) and ethyl acetate (3x 20 mL), dried over anhydrous sodium sulfate then the ethyl acetate was evaporated under vacuum. The crude product was recrystallized from ethanol gave the desired compounds.

**4-((8-hydroxyquinolin-5-yl)methyl)-N-phenylpiperazine-1-carbothioamide (5a)**



Off-White solid, (0.25 g, 67%); R*f* = 0.3 (Ethyl acetate); mp 205-207°C; IR (KBr, cm-1) 1535 (SO), 3233(NH), 3322 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.71 (s, 1H), 9.26 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.58 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 6.2 Hz, 4H), 7.07 (dd, *J* = 5.8, 3.2 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.82 (d, *J* = 4.7 Hz, 4H), 2.48 (q, *J* = 1.9 Hz, 4H). 13C NMR (101 MHz, DMSO-*d*6) δ 181.6, 153.4, 148.3, 141.5, 139.3, 134.3, 129.5, 128.5, 128.4, 128.3, 126.0, 125.6, 124.7, 124.1, 122.0, 110.4, 59.5, 52.8, 48.48. HRMS (ESI): m/z calcd for C21H21N4OS [M-H] 377.14361, found 377.13779.

**4-((8-hydroxyquinolin-5-yl)methyl)-N-(p-tolyl)piperazine-1-carbothioamide (5b)**



Off-White solid, (0.25 g, 64%); R*f* = 0.4 (Ethyl acetate); mp 193-195°C IR (KBr, cm-1) 1530 (SO), 3211(NH), 3402 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.74 (s, 1H), 9.20 (s, 1H), 8.84 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.66 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.57 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.82 (d, *J* = 4.8 Hz, 2H, -CH2-), 3.80 (s, 4H, 2x-CH2-), 2.44 (t, *J* = 4.9 Hz, 4H, 2x-CH2-), 2.24 (s, 3H, CH3). 13C NMR (101 MHz, DMSO-*d*6) δ 181.7, 153.4, 148.3, 139.3, 138.9, 134.2, 133.9, 1 29.5, 128.9, 128.3, 125.9, 124.1, 122.0, 110.4, 59.5, 52.8, 48.4, 21.0. HRMS (ESI): m/z calcd for C22H23N4OS [M-H] 391.15926, found 391.15981.

**N-(4-chlorophenyl)-4-((8-hydroxyquinolin-5-yl)methyl)piperazine-1-carbothioamide (5c)**



Off-White solid, (0.25 g, 62%); R*f* = 0.2 (Ethyl acetate); mp 224-226°C IR (KBr, cm-1) 1528 (CS), 3320(NH), 3436 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.74 (s, 1H), 9.34 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.66 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.58 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.33 – 7.24 (m, 4H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.82 (d, *J* = 5.8 Hz, 6H, 3x-CH2-), 2.45 (d, *J* = 5.3 Hz, 4H, 2x-CH2-). 13C NMR (101 MHz, DMSO-*d*6) δ 181.4, 153.4, 148.3, 140.5, 139.3, 134.2, 129.6, 128.6, 128.3, 128.3, 127.2, 124.1, 121.9, 110.4, 59.5, 52.7, 48.5. HRMS (ESI): m/z calcd for C21H20ClN4OS 411.10463, found 411.09675.

**4-((8-hydroxyquinolin-5-yl)methyl)-N-(4-nitrophenyl)piperazine-1-carbothioamide (5d)**



Yellow solid, (0.25 g, 60%); R*f* = 0.25 (Ethyl acetate); mp 170-172°C; IR (KBr, cm-1) 1530 (CS), 3150(NH), 3399 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.82 (s, 1H), 9.74 (s, 2H), 8.85 (d, *J* = 3.9 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 1H), 8.27 – 8.05 (m, 2H), 7.66 – 7.58 (m, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 3.84 (d, *J* = 12.2 Hz, 1H), 2.68 – 2.23 (m, 1H). 13C NMR (101 MHz, DMSO-*d*6) δ 180.8, 153.5, 148.3, 148.3, 142.3, 139.3, 134.2, 129.6, 128.3, 124.4, 123.2, 122.8, 122.0, 110.5, 61.2, 59.3, 52.7, 49.1. HRMS (ESI): m/z calcd for C21H21N5O3S [M-H] 423.13651, found 422.12923.

**N-(2-fluorophenyl)-4-((8-hydroxyquinolin-5-yl)methyl)piperazine-1-carbothioamide (5e)**



Beige solid, (0.25 g, 64%); R*f* = 0.25 (Ethyl acetate); mp 161-163°C; IR (KBr, cm-1) 1532 (CS), 3164(NH), 3304 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.74 (br s, 1H), 9.10 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.59 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.07 (m, 4H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.83 (d, *J* = 8.8 Hz, 6H), 2.46 (s, 4H). 13C NMR (101 MHz, DMSO-*d*6) δ 182.2, 157.8 (d, *1 JC-F* = 246 Hz), 153.4, 148.3, 139.3, 134.2, 130.0 (d, *2 JC-F* = 11 Hz), 129.3 (d, *3 JC-F* = 4 Hz), 128.2 (d, *3 JC-F* = 8.0 Hz), 124.5 (d, *4 JC-F* = 3 Hz), 122.0, 116.1 (d, *2 JC-F* = 20 Hz), 110.5, 59.5, 52.7, 48.4. HRMS (ESI): m/z calcd for C21H20FN4OS [M-H] 395.13419, found 395.13473.

**N-(3-fluorophenyl)-4-((8-hydroxyquinolin-5-yl)methyl)piperazine-1-carbothioamide (5f)**



White solid, (0.29 g, 74%); R*f* = 0.35 (Ethyl acetate); mp 206-208°C IR (KBr, cm-1) 1537 (CS), 3225(NH), 3321 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.74 (s, 2H), 9.39 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.66 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.58 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.28 (td, *J* = 8.2, 6.8 Hz, 1H), 7.19 (m,1H), 7.09 (m, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.93 – 6.84 (m, 1H), 3.82 (d, *J* = 7.7 Hz, 4H), 2.45 (d, *J* = 5.2 Hz, 4H). 13C NMR (101 MHz, DMSO-*d*6) δ 181.3, 161.2 (d, *1 JC-F* = 241 Hz), 153.4, 148.3, 143.4 (d, *3 JC-F* = 5 Hz), 139.3, 134.2, 129.9 (d, *4 JC-F* = 5 Hz), 129.6, 128.3, 124.1, 122.0, 120.8 (d, *3 JC-F* = 3. Hz), 112.0, 111.4 (d, *2 JC-F* = 24 Hz), 110.7 (d, *2 JC-F* = 20 Hz), 59.5, 52.7, 48.6. HRMS (ESI): m/z calcd for C21H20FN4OS [M-H] 395.13419, found 395.13461.

**N-(4-fluorophenyl)-4-((8-hydroxyquinolin-5-yl)methyl)piperazine-1-carbothioamide (5g)**



White solid, (0.35 g, 90%); R*f* = 0.2 (Ethyl acetate); mp 235-237 °C; IR (KBr, cm-1) 1538 (CS), 3241(NH), 3321 (OH); 1H NMR (400 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.29 (s, 1H), 8.83 (d, *J* = 4.1 Hz, 1H), 8.65 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.40 – 7.17 (m, 3H), 7.09 (t, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.83 (s, 4H), 3.79 (s, 2H), 2.44 (t, *J* = 4.7 Hz, 4H).13C NMR (101 MHz, dmso) δ 181.7, 159.6 (d, *1 JC-F* = 240 Hz), 153.4, 148.3, 139.3, 137.8 (d, *4 JC-F* = 2.0 Hz), 134.2, 129.5, 128.3, 128.1 (d, *3 JC-F* = 8.0 Hz), 124.1, 122.0, 115.0 (d, *2 JC-F* = 23 Hz), 110.4, 59.5, 52.7, 48.4. HRMS (ESI): m/z calcd for C21H20FN4OS [M-H] 395.13419, found 395.13466.

**4-((8-hydroxyquinolin-5-yl)methyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carbothioamide (5h)**



White solid, (0.40 g, 91 %); R*f* = 0.4 (Ethyl acetate); mp 191-193; IR (KBr, cm-1) 1535 (CS), 3172(NH), 3311 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.75 (s, 1H), 9.56 (s, 1H), 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.66 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.64 – 7.55 (m, 3H), 7.52 – 7.45 (m, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.84 (m, 4H), 3.81 (s, 2H), 2.46 (m, 4H). 13C NMR (101 MHz, DMSO-*d*6) δ 181.3, 153.4, 148.2, 148.2, 145.4, 139.3, 134.2, 129.5, 128.3, 126.3, 125.6, 125.5, 125.5, 125.5, 124.5, 124.4, 124.2, 124.1, 123.9, 123.6, 121.9, 110.4, 59.5, 52.7, 48.8. HRMS (ESI): m/z calcd for C22H22F3N4OS [M+H] 447.14664, found 447.14609.

**4-((8-hydroxyquinolin-5-yl)methyl)-N-(p-tolyl)piperazine-1-carboxamide (6b)**



White solid, (0.25 g, 66%); R*f* = 0.3 (Ethyl acetate); mp 168-170°C; IR (KBr, cm-1) 1637 (CO), 3337(NH), 3435 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.72 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.66 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.35 (s, 1H), 7.58 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.99 (dd, *J* = 7.9, 5.8 Hz, 3H), 3.78 (s, 2H), 2.38 (t, *J* = 5.1 Hz, 4H), 2.19 (s, 3H, CH3). 13C NMR (101 MHz, DMSO-*d*6) δ 155.0, 153.5, 148.0, 139.1, 138.8, 134.3, 133.8, 1 29.4, 128.9, 128.2, 125.7, 124.1, 122.0, 110.4, 59.7, 52.9, 48.5, 20.9. HRMS (ESI): m/z calcd for C22H23N4O2 [M-H] 375.18210, found 375.18265.

**N-(4-chlorophenyl)-4-((8-hydroxyquinolin-5-yl)methyl)piperazine-1-carboxamide (6c)**



Off-White solid, (0.31 g, 80%); R*f* = 0.4 (Ethyl acetate); mp 187-191°C; IR (KBr, cm-1) 1642 (CO), 3259(NH), 3434 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.74 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.65 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.61 (s, 1H), 7.57 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.20 (m, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 2H), 2.39 (t, *J* = 4.9 Hz, 4H). 13C NMR (101 MHz, DMSO-*d*6) δ 155.1, 153.4, 148.3, 140.0, 139.3, 134.2, 129.5, 128.6, 128.3, 125.7, 124.2, 121.9, 121.4, 110.4, 59.9, 52.9, 44.2. HRMS (ESI): m/z calcd for C21H20ClN4O2 [M-H] 395.12748, found 395.12803.

**4-((8-hydroxyquinolin-5-yl)methyl)-N-(4-nitrophenyl)piperazine-1-carboxamide (6d)**



White solid, (0.24g, 60%); R*f* = 0.25 (Ethyl acetate); mp 200-202°C; IR (KBr, cm-1) 1659 (CO), 3209(NH), 3300 (OH); 1H NMR (400 MHz, DMSO-*d*6) δ 9.75 (s, 1H), 9.21 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.22 – 8.04 (m, 2H), 7.84 – 7.64 (m, 2H), 7.57 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.79 (s, 2H), 3.42 (d, *J* = 5.3 Hz, 5H), 2.41 (t, *J* = 5.0 Hz, 4H). 13C NMR (101 MHz, DMSO-*d*6) δ 154.4, 148.3, 147.9, 141.2, 139.3, 134.3, 129.5, 128.3, 125.2, 121.9, 118.7, 110.4, 59.8, 52.9, 44.4. HRMS (ESI): m/z calcd for C21H20N5O4 [M-H] 406.15153, found 406.15208.