Supporting Information

An operational transformation of 3-carboxy-4-quinolones into 3-nitro-4-quinolones via ipso-nitration using polysaccharide supported copper nanoparticles: synthesis of 3-tetrazolyl bioisosteres of 3-carboxy-4-quinolones as antibacterial agents

Chandra S Azad and Anudeep K Narula*

“Hygeia” Centre of Excellence in Pharmaceutical Sciences (CEPS), GGS Indraprastha University, Sec. 16-C, Dwarka, New Delhi, India, E-mail: medchemlab58@gmail.com
General Information

Reagent grade solvents were used for the extraction and flash chromatography. All the reagents and chemicals were purchased from Sigma Aldrich Chemical Co., Merck and were used directly without further purification. The progress of reactions was checked by analytical thin-layer chromatography (TLC, Merck silica gel 60F-254 plates). The plates were visualized by UV illumination. Column chromatography was performed using silica gel (60-120 mesh). The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. All glassware’s were dried oven before use in connection with an inert atmosphere. Solvents were evaporated under reduced pressure. Tetramethylsilane (0.0 ppm) was used as an internal standard in $^1$H NMR and CDCl$_3$ (77.0 ppm) was used in $^{13}$C NMR. The abbreviations used to indicate the peak multiplicity were; s, singlet; bs, broad singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; Hz, Hertz. FAB MS was recorded on Jeol (Japan)/SX-102. Infrared spectrum was taken with ATR on Shimadzu IR-affinity-1s. Melting points were determined on a Buchi 565 digital melting point apparatus and were uncorrected.

Experimental procedure:

Synthesis of Polysac-Cu-NP

For the preparation of Plysac-Cu-NP cellulose and starch used as such but chitosan grind to very fine powder in mortar and pastel prior to use. The polysaccharide (1gm) were suspended in de-ionised water and sonicated at 40 kHz for 20 min. To polysaccharide suspension copper sulphate (250 mg) was added. The reaction mixture was stirred for 15 min under nitrogen atmosphere at room temperature and then cooled to 0°C by ice bath. The polysaccharide copper suspension carefully reduced by sodium borohydride (100 mg) in small portion with short interval of time. The black reaction mixture was again stirred for 1 hr till the temperature reached to rt. The black suspension again sonicated for about 15 min before filtration. The solid black mass washed with de-ionised water, vacuumed dried and stored under nitrogen atmosphere.
### ED-XRF report of chit-cu-NP synthesized

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### ED-XRF report of chit-cu-NP after fifth cycle

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Typical experimental procedure for the synthesis of 3-nitro-4-quinolone: In a typical experiment, the quinolone acid (7) (1 mmol), Chit-Cu-NP (37 mg, 5 mol %) and nitronium tetrafluoroborate (1.2 mmol) were taken in 50 ml round-bottom flask containing DMF (10 mL) and the reaction mixture was refluxed, till the completion of the reaction (monitored by TLC). After completion the reaction mixture was vacuum and extracted with ethyl acetate (25 ml x3) after addition of de-ionised water (50 ml), the collected EtOAc dried over sodium sulphate and evaporated under vacuum to give crude product (7). Crude was purified by silica gel (60-120 mesh) column chromatography to afford the corresponding product.

7-chloro-1-ethyl-6-fluoro-3-nitroquinolin-4(1H)-one (7a)

Yield: 92 %; pale yellow solid; mp 270-272°C (uncorrected). IR (v_max, ATR, cm⁻¹): 3444, 3278, 1660, 1434, 1309, 1249, 839, 456, 180. ¹H NMR (300 MHz, CDCl₃) δ 9.71 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 5.9 Hz, 1H), 4.50 (q, J = 6.9 Hz, 2H), 1.56 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃ + DMSO_d₆) δ 162.94 (d, J = 6.5 Hz), 157.95 (s), 152.75 (s), 146.18 (s), 135.61 (d, J = 8.5 Hz), 131.89 (s), 126.12 (m), 117.85 (d, J = 11 Hz), 113.22, 112.82, 48.66 (s), 13.64 (s). ES-MS (M+H): 271.0 m/z.

7-chloro-6-fluoro-1-isopropyl-3-nitroquinolin-4(1H)-one (7b)

Yield 85%; pale yellow solid; mp 263-256°C (uncorrected). IR (v_max, ATR, cm⁻¹): 3432, 3258, 1655, 1480, 1320, 1232, 842, 460; ¹H NMR (300 MHz, CDCl₃) δ 9.69 (s, 1H), 8.11 (m, 1H), 7.70 (dd, J = 3.4, 2.5 Hz, 1H), 4.74 (m, 1H), 1.56 (m, 7H); ¹³C NMR (100 MHz, CDCl₃ + DMSO_d₆) δ 162.88 (d, J = 8.7 Hz), 157.98 (s), 152.78 (s), 147.24 (s), 137.47 (d, J = 8.5 Hz), 132.12(s), 127.80 (d, J = 10 Hz), 126.19, 125.82, 118.89 (d, J = 13 Hz), 113.08, 112.69, 54.41 (s), 19.83 (s). ES-MS (M+H): 285.0 m/z.

1-butyl-7-chloro-6-fluoro-3-nitroquinolin-4(1H)-one (7c)

1. Note: All the precursors were synthesized according to the published literature. (Koga, H.; Itoh A.; Murayama, S.; Suzue S. and Irikura T., J. Med. Chem.; 1980, 23, 1358)
Yield: 82%; pale yellow solid; mp 275-278°C (uncorrected). IR (ν\text{max}, ATR, cm\(^{-1}\)): 3465, 3262, 1652, 1474, 1322, 1232, 1211, 851. \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 9.66 (s, 1H), 8.13 (m, 1H), 7.79 (d, J = 5.7 Hz, 1H), 4.10 (t, J = 7.6 Hz, 2H), 1.81 (m, 2H), 1.59 (m, 2H), 1.10 (dd, J = 8.8, 5.6 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\) + DMSO\(_d_6\)) δ 162.83 (d, J = 6.5 Hz), 157.90 (s), 152.70 (s), 145.21 (s), 135.4 (d, J = 6.5 Hz), 131.70 (s), 126.37, 125.99, 124.60 (d, J = 11 Hz), 116.31 (d, J = 11 Hz), 113.26, 112.88, 48.21 (s), 29.21 (s), 18.99 (s), 13.28 (s). Anal. calcd for C\(_{13}\)H\(_{12}\)ClFN\(_2\)O\(_3\): C, 52.27; H, 4.05; N, 9.38; Found C, 52.21; H, 4.12; N, 9.21. ES-MS (M+H): 299.1 m/z.

1-(sec-butyl)-7-chloro-6-fluoro-3-nitroquinolin-4(1H)-one (7d)

Yield 85%; pale yellow solid; mp 265-270°C (uncorrected). IR (ν\text{max}, ATR, cm\(^{-1}\)): 3421, 3269, 1644, 1452, 1325, 1238, 867, 380, 190. \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 9.60 (s, 1H), 8.11 (m, 1H), 7.75 (d, J = 5.6 Hz, 1H), 4.78 (m, 1H), 1.48 (m, 2H), 1.17 (d, J = 6.1 Hz, 3H), 0.92 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\) + DMSO\(_d_6\)) δ 162.88 (d, J = 9 Hz), 157.63 (s), 152.43 (s), 145.59 (s), 137.97 (d, J = 9 Hz), 132.26 (s), 127.44 (d, J = 12 Hz), 126.25 (s), 125.88 (s), 118.92 (d, J = 11 Hz), 113.14 (s), 112.75 (s), 50.46 (s), 26.77 (s), 19.91 (s), 8.00 (s). Elemental Analysis calculated for C\(_{13}\)H\(_{12}\)ClFN\(_2\)O\(_3\): C, 52.27; H, 4.05; N, 9.38; Found C, 52.21; H, 4.12; N, 9.29. ES-MS (M+H): 299.1 m/z.

7-chloro-6-fluoro-1-methyl-3-nitroquinolin-4(1H)-one (7e)

Yield 79%; yellow solid; m.p. 198-200°C, IR (ν\text{max}, ATR, cm\(^{-1}\)): 3412, 1610, 1511, 1302, 1121, 1062, 541; \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 9.67 (d, J = 0.5 Hz, 1H), 8.15 (m, 1H), 7.87 (d, J = 5.5 Hz, 1H), 3.5 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\) + DMSO\(_d_6\)): δ 168.34 (d, J = 2.53 Hz), 156.97, 153.89, 151.37, 141.28 (d, J = 3 Hz), 127.48 (t, J = 20 Hz), 121.99 (d, J = 8.34 Hz), 115.0 (t, J = 7.64 Hz), 110.61 (d, J = 19.88 Hz), 38.23; ES-MS (M+H): 257.04 m/z.

7-chloro-1-cyclopropyl-6-fluoro-3-nitroquinolin-4(1H)-one (7f)
Yield 76%; yellow solid; m.p. 210-212°C. IR (v<sub>max</sub>, ATR, cm<sup>-1</sup>): 3310, 1643, 1555, 1363, 1122, 1069, 581; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.69 (s, 1H), 8.14 (d, J = 7.95 Hz, 1H), 7.73 (d, J = 5.64 Hz, 1H), 3.75 (m, 1H), 1.04 (d, J = 4.83 Hz, 2H), 0.84 (d, J = 2.43 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO <i>d<sub>6</sub> </i>): δ 168.35 (d, J = 2.93 Hz), 158.32, 158.67, 157.99, 155.47, 140.22 (d, J = 2.84 Hz), 127.97 (d, J = 19.76 Hz), 120.20 (d, J = 8.34 Hz), 119.34, 114.05 (d, J = 7.66 Hz, H), 113.01 (d, J = 1.73 Hz), 113.0, 40.13, 10.78; ES-MS (M+H): 283.12 m/z.

6,7-difluoro-3-nitro-1-propylquinolin-4(1H)-one (7g) Yield 86% pale yellow solid; mp 262-263°C (uncorrected). IR (v<sub>max</sub>, ATR, cm<sup>-1</sup>): 3286, 3050, 1644, 1534, 1454, 1311, 1211, 831. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.65 (m, 1H), 8.30 (t, J = 9.5 Hz, 1H), 7.42 (dd, J = 11.0, 6.5 Hz, 1H), 3.59 (t, J = 7.4 Hz, 2H), 1.55 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO <i>d<sub>6</sub> </i>): δ 161.32 (d, J = 9 Hz), 155.71 (s), 154.93 (s), 150.49 (d, J = 1.2 Hz), 150.11 (d, J = 2 Hz), 149.73 (s), 145.28 (s), 144.90 (m), 136.04 (m), 123.84 (m), 112.90 (d, J = 11 Hz), 112.52 (d, J = 11.5 Hz) 114.20 (d, J = 13 Hz) 104.01 (d, J = 13 Hz), 50.83 (s), 21.73 (s), 9.96 (s). ES-MS (M+H): 269.8 m/z.

1-(sec-butyl)-6,7-difluoro-3-nitroquinolin-4(1H)-one (7h) Yield 88%; yellow solid; mp 265-266°C (uncorrected). IR (v<sub>max</sub>, ATR, cm<sup>-1</sup>): 3286, 3050, 1644, 1534, 1454, 1311, 1211, 831. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.66 (s, 1H), 8.31 (t, J = 9.4 Hz, 1H), 7.43 (m, 1H), 4.79 (m, 1H), 1.49 (m, 2H), 1.17 (d, J = 6.0 Hz, 3H), 0.94 (d, J = 9.4, 5.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO <i>d<sub>6</sub> </i>): δ 161.23 (d, J = 6.5 Hz), 154.96 (s), 154.57 (s), 150.48 (s), 150.11 (s), 149.74 (s), 147.40 (d, J = 0.6 Hz), 145.43 (s), 145.1 (d, J = 0.5 Hz), 144.90 (d, J = 1 Hz), 136.68 (m), 132.20 (s), 124.36 (m), 122.75 (d, J = 11 Hz), 12.37 (d, J = 13 Hz), 105.05 (d, J = 14 Hz) 104.67 (d, J = 11.5 Hz), 50.29 (s), 27.38 (s), 19.73 (s), 8.00 (s). ES-MS (M+H): 283.0 m/z.

6,7-difluoro-3-nitro-1-pentylquinolin-4(1H)-one (7i) Yield 91%; pale yellow solid; mp 269-271°C (uncorrected). IR (v<sub>max</sub>, ATR, cm<sup>-1</sup>): 3406, 3209, 3109, 1648, 1551, 1469, 1325, 1212, 867. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.67 (s, 1H), 8.31 (t, J = 9.5 Hz, 1H), 7.58 (dd, J = 11.0, 6.4 Hz, 1H), 4.03 (t, J = 7.5 Hz,
2H), 1.30 (m, 6H), 0.87 (dd, J = 8.5, 4.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃ + DMSO₆) δ 161.21 (d, J = 9 Hz), 155.29 (s), 154.91 (s), 150.77 (s), 150.40 (s), 150.08 (s), 149.71 (d, J = 0.75 Hz), 145.58 (s), 145.33 (s), 145.19 (s), 135.35 (m), 131.63 (s), 122.01 (m), 122.85 (d, J = 11 Hz), 122.49 (d, J = 11 Hz), 102.55 (d, J = 11 Hz), 102.16 (d, J = 13 Hz), 48.55 (s), 30.54 (s), 27.94 (s), 21.15 (s), 12.30 (s). ES-MS (M+H): 297.1 m/z.

6,7-difluoro-3-nitro-1-octylquinolin-4(1H)-one (7j)

Yield 82% pale yellow solid; mp 276-279°C (uncorrected). IR (ν_max, ATR, cm⁻¹): 3434, 3221, 3089, 1659, 1532, 1473, 1362, 1239, 856. ¹H NMR (300 MHz, CDCl₃) δ 9.67 (s, 1H), 8.31 (t, J = 9.5 Hz, 1H), 7.59 (dd, J = 11.0, 6.4 Hz, 1H), 4.04 (dd, J = 11.5, 4.1 Hz, 2H), 1.42 (m, 2H), 1.22 (m, 10H), 0.84 (m, 3H); ¹³C NMR (100 MHz, CDCl₃ + DMSO₆) δ 161.19 (d, J = 9 Hz), 155.26 (s), 154.88 (s), 150.76 (s), 150.39 (s), 150.07 (s), 149.68 (s), 145.95 (s), 145.56 (s), 145.18 (s), 135.36 (m), 131.62 (s), 122.02 (m), 112.85 (d, J = 13 Hz), 112.48 (d, J = 13 Hz), 102.52 (d, J = 11 Hz), 102.14 (d, J = 11 Hz), 49.77 (s), 30.40 (s), 28.68 (s), 28.59 (s), 27.71 (s), 26.67 (s), 21.91 (s), 13.37 (s); ES-MS (M+H): 339.1 m/z.

6,7-dichloro-1-ethyl-3-nitroquinolin-4(1H)-one (7k)

Yield 79%; pale yellow solid; mp 266-267°C (uncorrected). IR (ν_max, ATR, cm⁻¹): 3421, 3211, 3090, 1651, 1512, 1485, 1352, 1231, 856, 660; ¹H NMR (300 MHz, CDCl₃) δ 9.82 (s, 1H), 8.49 (s, 1H), 7.97 (s, 1H), 4.53 (q, J = 6.7 Hz, 2H), 1.56 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃ + DMSO₆) δ 163.41, 146.26, 136.80, 136.45, 132.07, 129.76, 128.04, 126.82, 117.46, 48.05, 13.65. ES-MS (M+H): 286.9 m/z.

6,7-dichloro-1-cyclopropyl-3-nitroquinolin-4(1H)-one (7l)

Yield 75% pale yellow solid; mp 271-271°C (uncorrected). IR (ν_max, ATR, cm⁻¹): 3440, 3321, 3101, 1644, 1521, 1467, 1331, 1242, 866, 649; ¹H NMR (300 MHz, CDCl₃) δ 9.79 (s, 1H), 8.47 (s, 1H), 7.89 (s, 1H), 3.67 (dd, J =
2.9, 1.9 Hz, 1H), 1.02 (m, 2H), 0.82 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO$_d_6$) δ 163.01, 147.23, 136.17, 135.26, 132.60, 129.79, 127.79, 127.75, 118.75, 33.42, 10.32. ES-MS (M+H): 298.9 m/z.

**1-butyl-6,7-dichloro-3-nitroquinolin-4(1H)-one (7m)**

Yield 79%; yellow solid; 268-270°C (uncorrected). IR ($v_{max}$, ATR, cm$^{-1}$): 3412, 3287, 3089, 1639, 1532, 1471, 1328, 1220, 869, 598. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.77 (s, 1H), 8.49 (s, 1H), 7.95 (s, 1H), 4.13 (t, $J = 7.6$ Hz, 2H), 1.81 (m, 2H), 1.60 (m, 2H), 1.09 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO$_d_6$) δ 163.27, 145.26, 137.15, 136.48, 131.86, 129.70, 128.05, 125.14, 115.71, 47.60, 29.21, 18.96, 13.27. ES-MS (M+H): 315.02 m/z.

**1-(sec-butyl)-6,7-dichloro-3-nitroquinolin-4(1H)-one (7n)**

Yield 79%; pale yellow solid; mp 265-266°C (uncorrected). IR ($v_{max}$, ATR, cm$^{-1}$): 3367, 3298, 3083, 1661, 1541, 1469, 1373, 1249, 841, 582, 421. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.71 (s, 1H), 8.45 (s, 1H), 7.97 (s, 1H), 4.79 (m, 1H), 1.49 (m, 2H), 1.16 (d, $J = 6.1$ Hz, 3H), 0.91 (dd, $J = 9.6$, 5.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO$_d_6$) δ 163.30, 145.65, 137.82, 136.37, 132.45, 129.43, 128.00, 127.96, 118.37, 49.83, 26.76, 19.90, 8.01; ES-MS (M+H): 315.02 m/z.

**6,7-dichloro-1-heptyl-3-nitroquinolin-4(1H)-one (7o)**

Yield 89%; pale yellow solid; mp 280-282°C (uncorrected). IR ($v_{max}$, ATR, cm$^{-1}$): 3421, 3321, 3211, 3108, 1659, 1488, 1392, 1241, 860, 637, 487. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.75 (m, 1H), 8.48 (s, 1H), 7.95 (s, 1H), 4.10 (td, $J = 7.5$, 0.6 Hz, 2H), 1.45 (m, 4H), 1.21 (m, 6H), 0.85 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO$_d_6$) δ 163.25, 146.18, 137.11, 136.47, 131.86, 129.69, 128.05, 125.13, 115.70, 48.26, 30.99, 27.78, 27.32, 26.65, 21.98, 13.37. ES-MS (M+H): 357.07 m/z.

**1-benzyl-7-chloro-6-fluoro-3-nitroquinolin-4(1H)-one (10a)**

Yield 52%; orange yellow; mp 244-246°C (uncorrected). IR ($v_{max}$, ATR, cm$^{-1}$): 3461, 3311, 3286, 3124, 1599, 1488, 1342. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.70 (s, 1H), 8.15 (d, $J = 7.74$ Hz, 1H), 7.58-7.43 (m, 1H), 7.41-7.16 (m, 2H),
7.16-6.90 (m, 1H), 5.58 (s, 2H) $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO$_d$$_6$) $\delta$ 168.34 (d, $J$ = 2.93 Hz), 155.90, 155.39, 152.86, 138.78 (d, $J$ = 3 Hz), 136.46, 127.76 (d, $J$=27.45 Hz), 127.32 (d, $J$ = 16.84 Hz), 120.02 (d, $J$ = 8.11 Hz), 116.97 (d, $J$ = 7.6 Hz), 112.04, 110.45 (d, $J$ = 21.08 Hz), 53.56. ES-MS (M+H): 333.62 m/z.

7-chloro-6-fluoro-3-nitro-1-(4-nitrobenzyl)quinolin-4(1H)-one (10b)

Yield 22%; canary yellow; mp 256-285°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.7 (s, 1H), 8.36-8.03 (m, 3H), 7.71-7.46 (m, 3H), 5.67 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO$_d$$_6$) $\delta$ 168.35 (d, $J$ = 2.93 Hz), 155.91, 155.40, 152.87, 144.87, 144.23, 138.79 (d, $J$ = 3 Hz), 127.66 (d, $J$ = 6.78 Hz), 127.42, 122.92, 122.88, 120.03 (d, $J$ = 8.11 Hz), 116.98 (d, $J$ = 7.61 Hz), 112.05, 110.46 (d, $J$ = 19.69 Hz, H), 53.57. ES-MS (M+H): 378.07 m/z.

General method for the preparation of 7-chloro-6-fluoro-1-methyl-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one

To a pre-cooled solution of 8 (4 mmol) in conc. HCl (25 ml) was added portion wise anhydrous SnCl$_4$ (3.5 equivalent) with vigorous stirring. The resulting mixture was then allowed to rt, and stirring was continued for additional 4 h. Afterward, the reaction mixture was diluted with cold water (25ml), basified with 40 % cold aq. NaOH solution to pH ~ 12-14. The precipitated solid product was collected by suction filtration, washed with cold water, dried and recrystallized from ethanol to give 3-amine derivative, which was further purified by column chromatography using eluent 5% CH$_3$OH/CHCl$_3$. 10 mmole of 3-amine derivative was dissolved in 25 ml of glacial acetic acid and to that 11mmol of NaN$_3$ and 12 mmole of triethyl orthoformate were added and the resultant reaction mixture was heated to 100-110°C for 7-8 h. The flow of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice (100gm) and the solid was filtered, washed with water and dried under vacuum to yield 12 in good yield.

7-chloro-6-fluoro-1-methyl-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14a)

Yield 82%; yellow solid; m.p. 252-253°C, IR (vmax, ATR, cm$^{-1}$): 3417, 1608, 1534, 1300, 1122, 1012, 563; NMR (300 MHz, CDCl$_3$): $\delta$ 4.57 (s,
3H), 8.16 (d, J=8Hz, 1H), 7.22 (d, J=6 Hz), 8.19 (d, J=8Hz), 9.55 (s, 1H), 9.64 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 43.83, 111.69, 114.38, 114.74, 117.53, 117.65, 125.34, 125.46, 126.9, 127.29, 129.43, 138.01, 140.39, 140.47, 153.51, 158.71, 175.69, 175.77; ES-MS (M+H): 280.04 m/z.

7-chloro-1-cyclopropyl-6-fluoro-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14b)

Yield 82%; yellow solid; m.p. 268-270°C, IR (vmax, ATR, cm$^{-1}$): 3409, 1605, 1532, 1304, 1115, 1043, 564; NMR (300 MHz, CDCl$_3$): δ 1.97–1.88 (m, 4H), 4.10-4.11 (m, 1H), 7.22 (d, J=6 Hz), 8.20 (d, J=8Hz), 9.55 (s, 1H), 9.64 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 8.43, 35.44, 112.46, 113.96, 114.33, 120.06, 120.18, 126.49, 126.86, 127.54, 127.69, 136.01, 136.09, 137.81, 153.57, 158.74, 175.22, 175.3; ES-MS (M+H): 306.05 m/z.

7-chloro-1-ethyl-6-fluoro-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14c)

Yield 82%; yellow solid; m.p. 277-278°C, IR (vmax, ATR, cm$^{-1}$): 3410, 1605, 1580, 1318, 1122, 1022, 582; NMR (300 MHz, CDCl$_3$): δ 1.42 (t, 3H), 4.48 (d, J=6.8 Hz), 7.25 (d, J=6 Hz), 8.19 (d, J=8Hz), 9.55 (s, 1H), 9.64 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 10.7, 49.22, 111.92, 114.24, 114.61, 118.59, 118.69, 126.22, 126.35, 126.77, 127.14, 128.6, 136.63, 136.7, 137.32, 153.53, 158.74, 175.62, 175.7; ES-MS (M+H): 294.8 m/z.

7-chloro-6-fluoro-1-isopropyl-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14d)

Yield 82%; yellow solid; m.p. 273-274°C, IR (vmax, ATR, cm$^{-1}$): 3410, 1608, 1484, 1322, 1119, 1025, 566; NMR (300 MHz, CDCl$_3$): δ 1.55 (6H), 4.93 (s, 1H), 7.25 (d, J=6 Hz), 8.19 (d, J=8Hz), 9.55 (s, 1H), 9.64 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 16.87, 56.12, 112.14, 114.1, 114.48, 119.61, 119.73, 126.62, 127.01, 127.08, 127.2, 127.77, 137.96, 138.13, 138.2, 153.56, 158.76, 175.54, 175.61; ES-MS (M+H): 308.8 m/z.
General method for the preparation of 6-fluoro-1-alkyl-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one

4 mmol of 8 was taken in a round bottom flask having 20 mm of DMSO in which 6 mmol of piperazine was added and reaction mixture was allowed to stirrer at 120-130°C for about 9-10h. After completion of reaction as evidenced by TLC, DMSO was removed in vacuum and reaction mixture partitioned in between DCM and water. DCM layer was successively wased with 0.5 N HCl (20 ml), water (20ml X 3) and finally with brine. The DCM layer on vacuum evaporation yield crude 11 which was further purified by column chromatography using eluent 40% EtOAc/Hexane. After getting 11 same method was applied as used for the synthesis of 12a-d to yield 11a-d in good yield.

6-fluoro-1-methyl-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13a)

Yield 82%; light brown solid; m.p. 326-322°C, IR (vmax, ATR, cm-1): 3412, 1603, 1484, 1322, 1122, 1023, 756, 583; NMR (300 MHz, CDCl₃+DMSO-d₆): δ 3.14 (m, 4H), 3.50 (m, 4H), 4.02 (bs, NH), 4.52 (s, 3H), 6.60 (d, J=6.73 Hz, 1H), 7.83 (d, J=12.6 Hz, 1H), 9.50 (s, 1H), 9.59 (s, 1H); ¹³C NMR (75 MHz, CDCl₃+DMSO-d₆): δ 43.99, 45.1, 49.9, 49.99, 102.85, 102.98, 107.47, 112.48, 112.87, 121.33, 121.46, 129.36, 138.02, 141, 141.08, 144.59, 144.96, 150.06, 155.25, 175.06, 175.14; ES-MS (M+H): 330.2 m/z.

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13b)

Yield 82%; light brown solid; m.p. 336-334°C, IR (vmax, ATR, cm-1): 3414, 1599, 1481, 1319, 1119, 1033, 777, 576; NMR (300 MHz, CDCl₃+DMSO-d₆): δ 0.98 (m, 2H), 1.13 (m, 2H), 3.10 (m, 4H), 3.44 (m, 4H), 4.05 (bs, NH), 7.57 (s, 1H), 7.84 (d, J=6.5 Hz), 9.51 (s, 1H), 9.60 (s, 1H); ¹³C NMR (75 MHz, CDCl₃+DMSO-d₆): δ 6.78, 33.55, 45.1, 49.9, 49.98, 106.56, 106.68, 108.24, 112.06, 112.44, 122.68, 122.81, 127.64, 137.82, 138.76, 138.83, 143.18, 143.56, 150.1, 155.28, 174.6, 174.68; ES-MS (M+H): 356.3 m/z.

1-ethyl-6-fluoro-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13c)
Yield 82%; light brown solid; m.p. 356°C, IR (vmax, ATR, cm-1): 3408, 1402, 1321, 1131, 1028, 802, 566; NMR (300 MHz, CDCl₃+DMSO-d₆): δ 1.44 (t, 2H), 3.15 (m, 4H), 3.51 (m, 4H), 4.08 (bs, NH), 4.50 (dd, 2H), 7.02 (d, J=6Hz, 1H), 7.88 (d, J=12.5Hz, 1H), 9.56 (s, 1H), 9.67 (s, 1H); ¹³C NMR (75 MHz, CDCl₃+DMSO-d₆): δ 10.93, 45.1, 48.79, 49.9, 49.97, 104.18, 104.28, 107.7, 112.34, 112.74, 121.79, 121.91, 128.52, 137.32, 138.73, 138.8, 144.97, 145.36, 150.08, 155.27, 174.99, 175.06; ES-MS (M+H): 344.3 m/z.

6-fluoro-1-isopropyl-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13d)

Yield 82%; light brown solid; m.p. 348-349°C, IR (vmax, ATR, cm-1): 3422, 1610, 1490, 1304, 1132, 1042, 768, 595; NMR (300 MHz, CDCl₃): δ 1.47 (m, 6H), 3.05 (m, 4H), 3.43 (m, 4H), 3.98 (bs, NH, 4.85 (m, 1H), 7.52 (s, 1H), 7.76 (m, 1H), 9.46 (s, 1H), 9.55 (s, 1H); ¹³C NMR (75 MHz, CDCl₃+DMSO-d₆): δ 17.1, 45.11, 49.89, 49.98, 55.88, 106.11, 106.23, 107.92, 112.22, 112.6, 122.22, 122.34, 127.71, 137.98, 141.69, 141.76, 143.33, 143.71, 150.1, 155.3, 174.91, 175; ES-MS (M+H): 358.2 m/z.
$^{1}H$ and $^{13}C$ NMR Spectra of compound 7a
$^1$H and $^{13}$C NMR Spectra of compound 7b
\(^1\text{H} \text{ and } ^{13}\text{C} \text{ NMR Spectra of compound 7c}\)
$^1$H and $^{13}$C NMR Spectra of compound 7d
$^1$H and $^{13}$C NMR Spectra of compound 7e
$^{1}H$ and $^{13}C$ NMR Spectra of compound 7f
$^1$H and $^{13}$C NMR Spectra of compound 7g
$^1$H and $^{13}$C NMR Spectra of compound 7h
$^1$H and $^{13}$C NMR Spectra of compound 7i
$^1$H and $^{13}$C NMR Spectra of compound 7j
$^1$H and $^{13}$C NMR Spectra of compound 7k
$^1$H and $^{13}$C NMR Spectra of compound 71
$^1$H and $^{13}$C NMR Spectra of compound 7m
$^1$H and $^{13}$C NMR Spectra of compound 7n
$^{1}H$ and $^{13}C$ NMR Spectra of compound 7o
$^1\text{H}$ and $^{13}\text{C}$ NMR Spectra of compound 10a
$^1$H and $^{13}$C NMR Spectra of compound 10b
$^1$H and $^{13}$C NMR Spectra of compound 13a
1H and 13C NMR Spectra of compound 13b
$^1$H and $^{13}$C NMR Spectra of compound 13c
$^1$H and $^{13}$C NMR Spectra of compound 13d
$^1$H and $^{13}$C NMR Spectra of compound 14a
$^1$H and $^{13}$C NMR Spectra of compound 14b
$^1$H and $^{13}$C NMR Spectra of compound 14c
$^{1}H$ and $^{13}C$ NMR Spectra of compound 14d
Method for biological evaluation

**Solvent Used:** DMSO

**Standard Antibiotic used:** Ciprofloxacin

**Concentrations screened:** 6.25, 12.5, 25, 50 and 100 µM

**Stock Sample Concentration:** 1 mM

**Name of the analysis method:** Micro-dilution method

**Bacteria analyzed:** *Staphylococcus aureus*, *Staphylococcus aureus (MRSA)*, *Escherichia coli*, *Salmonella typhi* and *Vibrio cholerae*

**Description:**

Media Used (Muller Hinton broth): Beef extract 2g; Casein hydrolysate 17.5g; Starch 1.5g in 1000 ml of distilled water. Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 37°C for 18 hrs. A 0.5ml culture was centrifuged and resuspended in 250µl volume of above sterile medium to obtain a 5x10^9 CFU/ml which was diluted to 5x10^5 CFU/ml. Ciprofloxacin was used as a standard and compounds (CSA001- CSA004) were added at the concentrations mentioned above. The bacterial solution (4x10^7 CFU/ml) was mixed well and this suspension was added to each well of microtitre plate so that the final volume of compounds and media reaches to 200 µl. The microtitre plate was incubated at 37°C for 24 h and bacterial growth was observed. The visual MIC was reached by comparing the turbidity with that of uninoculated broth. The complete visual similarity of test wells with that of uninoculated broth is considered as MIC.

Reference:

**Method for docking studies**

The molecular modelling study was performed with Molegro Virtual Docker (MVD) v 4.0.0 (www.molegro.com) along with Graphical User Interface (GUI), MVD tools was used to generate grid, calculate dock score and evaluate conformers. The scoring function used by MolDock is derived from the Piecewise Linear Potential (PLP) scoring functions. The active binding site was considered as a rigid molecule, whereas the ligands were treated as being flexible, that is, all non-
ring torsions were allowed. The structures of title compounds (13 and 14) were subjected to energy minimization using molecular mechanics (MM2). The minimization was performed until the root mean square (RMS) gradient value reached a value smaller than 0.001 kcal/mol. Finally the protein target (2XCT) was prepared for molecular docking simulation in such a way that all heteroatoms (i.e., non-receptor atoms such as water, ions, etc) were removed. The active binding site region was defined as a spherical region which encompasses all protein within 15.0 Å of bound crystallographic ligand atom. The docking protocol includes the grid resolution of 0.30, for grid generation and 15 Å radius from the template as the binding site. MolDock SE was used as a search algorithm and the number of runs was set to 10 Å population size of 50 and maximum interactions of 1500 were used for parameter settings. The maximum number of poses generated was 10. Since MVD works by an evolutionary algorithm, successive docking runs do not give precisely the same pose and interactions. To address this inherent randomness, three consecutive runs were done and the best three poses were used to visualize the interactions of all inhibitors.