

# Synthesis and Antimalarial Activity of 7-Chloro-4-(4-(2-(Oxo, Hydroxyl & Fluoro-2-1 (4-Phenyl)Ethyl)Piperazin-1-yl)Quinoline Derivatives

Akhil Mahajan <sup>1</sup>, Tejpal Singh Chundawat <sup>1,\*</sup>

<sup>1</sup> Department of Applied Sciences, The NorthCap University, India; akhil17asd003@ncuindia.edu (A.M.);

\* Correspondence: chundawatchem@yahoo.co.in (T.S.C.);

Scopus Author ID 55428754800

Received: 2.10.2021; Revised: 5.11.2021; Accepted: 9.11.2021; Published: 5.12.2021

**Abstract:** Since these days, microbes are resistant to the drugs available in the market, which has caused an alarming impact on society. 18 compounds in a series of 7-chloro-4-(piperazin-1-yl)quinoline derivatives were synthesized by nucleophilic addition reaction of piperazine with 4,7-dichloroquinoline followed by phenacyl bromides addition to heteroaryl piperazine and then reduction and fluorination. All 18 compounds were evaluated *in vitro* for their antimalarial activity against *plasmodium falciparum* strain. Although 12 compounds showed good activity, compound 3c was found to be more potent than standard drug Quinine having MIC 0.18 µg/ mL. On the other hand, 3d, 3e, 5a, and 5f were found to be equipotent (MIC 0.26 µg/ mL) to the standard drug.

**Keywords:** piperazine; quinoline, synthesis, antimalarial activity.

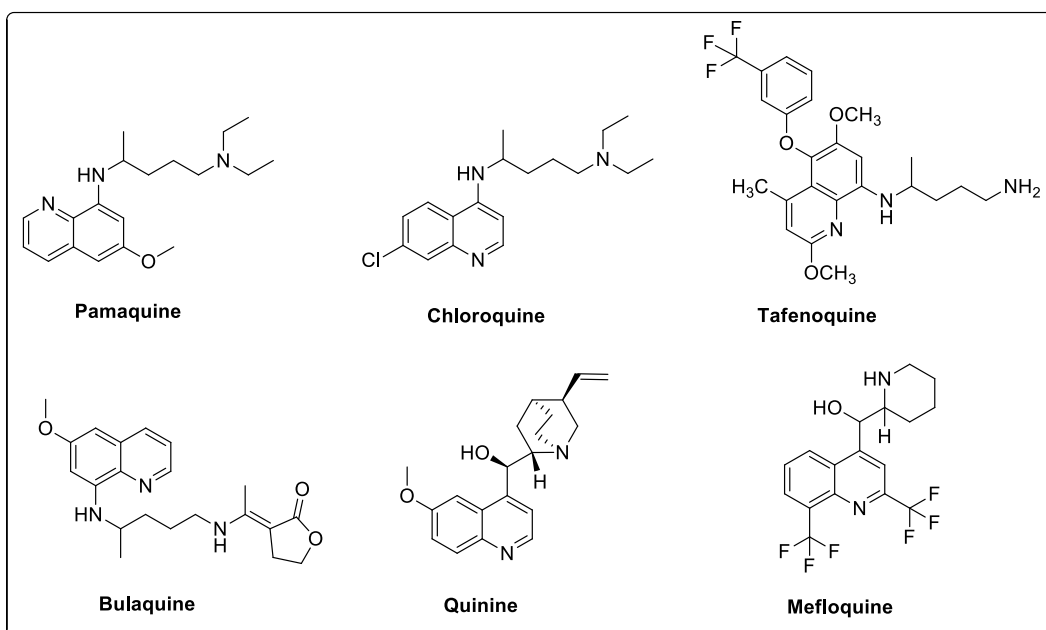
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## 1. Introduction

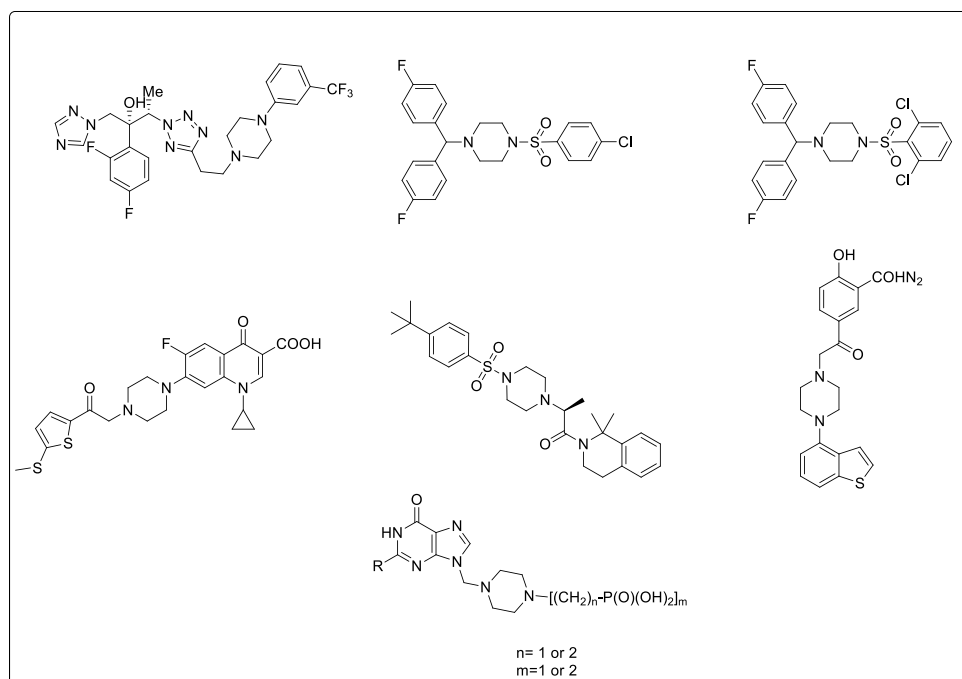
These days, microbes are resistant to the drugs available in the market, causing an alarming impact on society [1–6]. If no action is taken, by 2050, drug-resistant diseases can kill 10 million living beings each year, devastating effects on the economy. By 2030, antimicrobial resistance may force 24 million people to live below the poverty line. Drug-resistant diseases claim the lives of at least 700,000 individuals each year. [7]. The most common example in the medical world these days is the superbug. The wide applications of quinoline in the fields of therapeutic, bioorganic, modern science, and natural engineering sciences have always attracted scientists [8–10]. Quinoline derivatives have been discovered to have a variety of medicinal properties, including antimalarial [11–14], antibacterial, antifungal [15–17], antiviral [18], anticancer [19–22], antitubercular [23–26], etc. (Figure 1). Microorganisms have shown their adaption to the existing antibiotics. Therefore, there is always a need for new antimicrobial substances that must be active against drug-resistant microorganisms.

Another important class of biologically active compounds is piperazine. Its analogs are well-known nitrogen-containing heterocyclic with a variety of biological activities, such as antimicrobial [27–32], antiproliferative [33], and antidepressant [34].

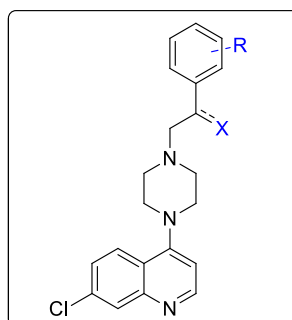
Various scaffolds of piperazine have been used to enhance antimalarial activity [35–37] (Figure 2). In the current research work, we have designed a prototype shown in Figure 3. Quinoline derivatives based on the prototype were synthesized and evaluated for antimalarial activity against *Plasmodium falciparum* strain.



**Figure 1.** List of various commercialized quinoline.



**Figure 2.** Antimalarial scaffolds with piperazine moiety.



R= 4-H, 4-OMe, 4-Cl, 4-F, 4-CN, 2,4-Cl  
X=-C=O,-OH,-F

**Figure 3.** Designed prototype.

## 2. Materials and Methods

Spectrochem and Aldrich Chemical Company provided all of the essential chemicals. For analytical thin-layer chromatography (TLC), pre-coated aluminum sheets (silica gel 60 F254, Merck) were utilized, and spots were seen under UV light. On an Agilent Technologies 400 MHz VNMRs spectrometer running at 400/100 MHz with DMSO as the internal standard, proton nuclear magnetic resonance ( $^1\text{H}$  NMR) and carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were acquired. Parts per million (ppm) are used to describe chemical shifts ( $\delta$ ). The coupling constants (J) are expressed in hertz (Hz). A Finnigan LCQ-Classic (ESI-MS; Thermo Separation Products, San José, USA) or an expression S compact mass spectrometer was used to obtain mass spectrometric data (APCI-MS; Advion Inc., Ithaca, USA).

### 2.1. General procedure for synthesis of 7-chloro-4-(piperazin-1-yl)quinoline (2).

To a solution of 4,7-dichloroquinoline (1.0 eq) in DIPEA (5v) at RT was added piperazine (2.0 eq). The reaction mass was heated at 110°C for a period of 16h. Completion of the reaction was confirmed by TLC. After completion of the reaction, the RM was allowed to warm to RT, and solid precipitation was observed. DIPEA was then decanted. Ethyl acetate / Water workup was done. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to obtain the crude material. The obtained crude material was slurred in hexane and filtered over Buchner funnel under reduced pressure to obtain desired, which was used for the next reaction.

*7-chloro-4-(piperazin-1-yl)quinoline (2)*. Off white solid, Yield : 50%; M.F.  $\text{C}_{13}\text{H}_{14}\text{ClN}_3$ ; M.W. 247.72; M.P. 105–110 °C ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz):  $\delta$  8.69 (d, J=4.8 Hz, 1H), 8.03 (d, J=8.8 Hz, 3H), 7.96 (s, 1H), 7.56–7.53 (d, J=9.2 Hz, 2H), 6.98 (d, J=5.2 Hz, 1H), 3.08 (s, 4H,  $-\text{CH}_2$  piperazine), 2.96 (s, 4H,  $-\text{CH}_2$  piperazine);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  157.45 (1C), 152.03(1C), 150.18(1C), 134.94(1C), 128.89(1C), 126.20(1C), 125.32(1C), 122.00(1C), 109.05(1C), 53.55(2C, piperazine), 46.09(2C, piperazine); EI-MS,  $m/z$ : 248.00  $[\text{M}+\text{H}]^+$ .

### 2.2. General procedure for synthesizing compounds (3a–3f).

To a solution of heteroaryl piperazine (1.0 mol eq.) in DMF (20V) was added potassium carbonate (2.0 eq), and the mixture was cooled to 0–5 °C. Phenacyl bromide (1.0 mol eq.) was dissolved in DMF (3v) and added dropwise at 0–5 °C. The reaction mass was stirred at the same temperature for 6–8h. Reaction progress was monitored on TLC using Ethyl acetate (100%) as mobile phase and seen in a UV light (254nm). After completion of the reaction, the reaction mass was quenched with wet ice water. Ethyl acetate / Water workup was done. Layers were separated. The organic layer was then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to obtain the crude material. The obtained crude material was purified by column chromatography using 100–200 mesh silica and Ethyl acetate / Hexane as a solvent system. The desired fractions were collected and distilled off at 45–50°C to obtain the required material (Yield: 91–95%).

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-phenylethanone (3a)*. Off white solid, Yield : 91%; M.F.  $\text{C}_{21}\text{H}_{20}\text{ClN}_3\text{O}$ ; M.W. 366.48; M.P. 95°–100°C ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400MHz):  $\delta$  8.70 (d, J=4.8 Hz, 1H), 8.03 (d, J=8.00 Hz, 3H), 7.98 (s, 1H), 7.67 (t, J=7.2 Hz, 1H), 7.57–7.52 (m, 3H), 7.02 (d, J=4.8 Hz, 1H), 4.00 (s, 2H), 3.20 (s, 4H,  $-\text{CH}_2$  piperazine), 2.83 (s, 4H,  $-\text{CH}_2$  piperazine);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  195.1(1C, C=O), 155.9(1C), 150.8(1C), 148.9(1C), 134.8(1C), 133.8(1C), 132.4(1C), 127.7(2C), 127.6(2C), 125.1(1C), 124.1(1C),

120.8(1C), 108.0(1C), 63.1(1C), 52.2 (2C, piperazine), 50.9 (2C, piperazine); EI-MS,  $m/z$ : 366.10 [M+H]<sup>+</sup>.

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-(4-methoxyphenyl)ethanone (3b)*. Off white solid, Yield: 91%; M.F. C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub>; M.W. 395.14; M.P. 80°–85°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.69 (d, J=4.00Hz, 1H), 8.02 (d, J=8.00 Hz, 2H), 7.94 (s, 1H), 7.57–7.54 (m, 1H), 7.06–6.98 (m, 4H), 3.90 (s, 2H), 3.82 (s, 3H, -OCH<sub>3</sub>), 3.20 (s, 4H, -CH<sub>2</sub> piperazine), 2.81 (s, 4H, -CH<sub>2</sub> piperazine), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 194.7(1C, C=O), 163.8(1C), 157.80(1C), 156.02(1C), 150.96(1C), 149.01(1C), 133.56(1C), 129.36(1C), 128.71(2C), 127.54(1C), 124.89(1C), 124.56(1C), 120.90(2C), 112.60(1C), 108.04(1C), 61.26(1C, -CH<sub>2</sub>), 54.18(1C, OCH<sub>3</sub>), 51.75(2C, piperazine), 51.15(2C, piperazine); EI-MS,  $m/z$ : 396.30 [M+H]<sup>+</sup>.

*1-(4-chlorophenyl)-2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)ethanone (3c)*. Off white solid, Yield: 93%; M.F. C<sub>21</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O; M.W. 400.30; M.P. 130°–135°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (d, J=4.8Hz, 1H), 8.05–7.97 (m, 4H), 7.62 (d, J=8.40 Hz, 2H), 7.57–7.54 (m, 1H), 7.02 (d, J=5.2 Hz, 1H), 3.98 (s, 2H), 3.19 (s, 4H, -CH<sub>2</sub> piperazine), 2.81 (s, 4H, -CH<sub>2</sub> piperazine), Mass calculated- 400.30, <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): 195.23 (1C, C=O), 156.96(1C), 151.98(1C), 150.09(1C), 141.00(1C), 135.014(1C), 134.00(1C), 129.73(2C), 129.07(2C), 128.88(1C), 126.32(1C), 125.20(1C), 109.16(1C), 64.41(1C), 53.35(2C, piperazine), 52.07(2C, piperazine); EI-MS,  $m/z$ : 400.10 [M]<sup>+</sup>.

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-(4-fluorophenyl)ethanone (3d)*. Off white solid, Yield: 95%; M.F. C<sub>21</sub>H<sub>19</sub>ClFN<sub>3</sub>O; M.W. 383.84; M.P. 95°–100°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (d, J=4.8 Hz, 1H), 8.14–8.10 (m, 2H), 8.03–7.97 (m, 2H), 7.57–7.55 (m, 1H), 7.39 (t=8.8.80 Hz, 2H), 7.02 (d, J=4.8 Hz, 1H), 3.97 (s, 2H), 3.19 (s, 4H, -CH<sub>2</sub> piperazine), 2.81 (s, 4H, -CH<sub>2</sub> piperazine); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 194.79 (1C, C=O), 164.72(1C), 156.99(1C), 151.97(1C), 150.07(1C), 135.04(1C), 132.33(1C), 132.30(1C), 131.04(1C), 130.95(1C), 128.86(1C), 126.32(1C), 125.21(1C), 121.95(1C), 116.00(1C), 115.78(1C), 109.16(1C), 64.37(1C), 53.36(2C, piperazine), 52.08(2C, piperazine); EI-MS,  $m/z$ : 384.10 [M+H]<sup>+</sup>.

*4-(2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)acetyl)benzotrile (3e)*. Off white solid, Yield: 93%; M.F. C<sub>22</sub>H<sub>19</sub>ClN<sub>4</sub>O; M.W. 390.86; M.P. 175°–180°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (d, J=4.8 Hz, 1H), 8.17 (d, J=8.4 Hz, 2H), 8.03–7.97 (m, 4H), 7.57–7.55 (m, 1H), 7.02 (d, J=5.2 Hz, 1H), 4.04 (s, 2H), 3.19 (s, 4H, -CH<sub>2</sub> piperazine); 2.28 (s, 4H, -CH<sub>2</sub> piperazine); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 194.14 (1C, C=O), 155.79(1C), 150.81(1C), 148.90(1C), 137.62(1C), 133.99(2C), 131.49(2C), 127.71(1C), 125.27(1C), 124.04(1C), 120.79(1C), 116.84(1C), 115.66(1C), 108.06(1C), 63.61(1C), 52.21(2C, piperazine), 50.94(2C, piperazine); EI-MS,  $m/z$ : 391.25 [M+H]<sup>+</sup>.

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-(2,4-dichlorophenyl)ethanone (3f)*. Off white solid, Yield: 91%; M.F. C<sub>21</sub>H<sub>18</sub>Cl<sub>3</sub>N<sub>3</sub>O; M.W. 434.74; M.P. 125°–130°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.69 (d, J=4.80 Hz, 1H), 8.02–7.97 (m, 2H), 7.78–7.75 (m, 2H), 7.56 (t, J=8.40 Hz, 2H), 7.01 (d, J=4.80Hz, 1H), 3.86 (s, 2H), 3.15 (s, 4H, -CH<sub>2</sub> piperazine), 2.80 (s, 4H, -CH<sub>2</sub> piperazine); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125MHz): 198.65 (1C, C=O), 161.66(1C), 156.12(1C), 151.47(1C), 151.38(1C), 149.33(1C), 130.05(1C), 129.32(1C), 127.69(1C), 126.73(1C), 125.18(2C), 120.00(1C), 109.17(1C), 108.64(1C), 66.01(1C), 52.11(2C, piperazine), 51.37(2C, piperazine); EI-MS,  $m/z$ : 434.30 [M]<sup>+</sup>.

2.3. General procedure for synthesizing compounds (4a–4f).

The keto compound (3a–3f) (1.0 moleq.) was dissolved in Ethanol/THF (1:1, 20v), and the mixture was then cooled to 0–5°C. NaBH<sub>4</sub> (2.0 mol eq.) was added at 0–5°C, and then the reaction mixture was allowed to warm at ambient temperature and stirred for 2–4h. The progress of the reaction was monitored by TLC using Ethyl acetate/Hexane (1:1) as the mobile phase and seen in a UV light (254nm). After the reaction was completed, the pH was adjusted to 6.0 with acetic acid (0.4v) to quench the excess NaBH<sub>4</sub>. The reaction mass was then poured into DM water (20v) and extracted with dichloromethane (2×20v). All the organic layers were combined and distilled under reduced pressure at 40–45°C to obtain a crude oily residue. Obtained crude hydroxy product (4a–4f) was then purified by column chromatography using 100–200 mesh silica gel and 80% ethyl acetate/ hexane to pure ethyl acetate as solvent system. Pure fractions were collected and distilled off under reduced pressure at 45–50°C to obtain desired material (Yield 80–85%).

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-phenylethanol (4a)*. Off white solid, Yield: 85%; M.F. C<sub>21</sub>H<sub>22</sub>ClN<sub>3</sub>O; M.W. 367.87; M.P. 120°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (4.4 Hz, 1H), 8.02 (d, J=8.8 Hz, 1H), 7.97 (s, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.39 (d, J=7.2 Hz, 2H), 7.34–7.32 (m, 2H), 7.25 (d, J= 7.2 Hz, 1H), 7.00 (d, J=4.4 Hz, 1H), 5.10 (s, 1H), 4.78 (s, 1H), 3.18 (s, 4H, -CH<sub>2</sub> piperazine), 2.78 (S, 4H, -CH<sub>2</sub> piperazine), 2.64–2.59 (m, 1H), 2.53 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.75(1C), 150.90(1C), 149.05(1C), 140.74(1C), 133.91(1C), 127.85(1C), 127.43(2C), 126.67(1C), 125.21(1C), 124.84(2C), 124.07(1C), 120.83(1C), 108.03(1C), 67.85(1C, CHOH), 65.15(1C), 52.21(2C,piperazine), 51.20(2C,piperazine); EI-MS, *m/z*: 368.20 [M+H]<sup>+</sup>.

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-(4-methoxyphenyl)ethanol (4b)*. Gummy, Yield: 80%; M.F. C<sub>22</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>2</sub>; M.W. 397.89; M.P. 110–115°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (d, J=4.96 Hz, 1H), 8.00 (d, J=9.04Hz, 1H), 7.97 (s, 1H), 7.57–7.54 (m, 1H), 7.29 (d, J=8.4 Hz, 2H), 7.01 (d, J=4.96, 1H), 6.88 (d, J=8.56, 2H), 4.97(s, 1H), 4.72 (S, 1H), 3.73 (s, 3H, -OCH<sub>3</sub>), 3.18 (s, 4H, -CH<sub>2</sub> piperazine), 2.77 (s, 4H, -CH<sub>2</sub> piperazine), 2.63–2.57 (m, 1H), 2.53 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125MHz): δ 159.16(1C), 156.89(1C), 151.80(1C), 149.90(1C), 135.00(1C), 133.76(1C), 128.65(2C), 127.16(1C), 126.24(1C), 125.14(1C), 121.82(1C), 113.86(2C), 109.04(1C), 68.57(1C, CHOH), 66.17(1C), 55.29(1C,OCH<sub>3</sub>), 53.39(2C,piperazine), 52.19(2C,piperazine); EI-MS, *m/z*: 398 [M+H]<sup>+</sup>.

*1-(4-chlorophenyl)-2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)ethanol (4c)*. Off white solid, Yield: 84%; M.F. C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O; M.W. 402.31; M.P. 95–100°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (d, J=4.96 Hz, 1H), 8.02 (d, J=9.00Hz, 1H), 7.97 (s, 1H), 7.56 (d, J=9.00 Hz, 1H), 7.42–7.37 (m, 4H), 7.00 (d, J=5.00 Hz, 1H), 5.23 (s, 1H), 4.79 (s, 1H), 3.17 (m, 4H, -CH<sub>2</sub> piperazine), 2.77 (m, 4H, -CH<sub>2</sub> piperazine), 2.66–2.58 (m, 1H), 2.53 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.82(1C), 152.01(1C), 150.15(1C), 140.39(1C), 135.17(1C), 133.39(1C), 128.97(1C), 128.70(2C), 127.31(2C), 126.37(1C), 125.15(1C), 121.93(1C), 109.16(1C), 68.34(1C, CHOH), 66.11(1C), 53.39 (2C, piperazine), 52.29 (2C, piperazine); EI-MS, *m/z*: 402.50 [M]<sup>+</sup>.

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-(4-fluorophenyl)ethanol (4d)*. Off white solid, Yield: 82%; M.F. C<sub>21</sub>H<sub>21</sub>ClF<sub>2</sub>N<sub>3</sub>O; M.W. 385.86; M.P. 125–130°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ 8.70 (d, J=4.8 Hz, 1H), 8.02 (d, J=9.2 Hz, 1H), 7.97 (s, 1H), 7.56–7.54 (m, 1H), 7.43–7.39 (m, 2H), 7.14 (t, J=8.80 Hz, 2H), 7.00 (d, J=4.8 Hz, 1H), 5.17 (s, 1H), 4.80–4.76 (m, 1H), 3.17 (s, 4H, -CH<sub>2</sub> piperazine), 2.78 (s, 4H, -CH<sub>2</sub> piperazine), 2.63–2.58 (m, 1H), 2.52(m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 162.37 (d, J= 243.9 Hz,1C), 156.84 (1C), 152.01(1C), 150.15(1C),

137.53 (d,  $J = 2.8$  Hz, (1C)), 135.06(1C), 128.96(1C), 127.64 (d,  $J = 7.9$  Hz, (1C)), 126.36(1C), 125.16(1C), 121.94(1C), 115.4 (d,  $J = 21.3$  Hz, (1C)), 109.15(1C), 68.38(1C, -CHOH), 66.26(1C), 53.39(2C, piperazine), 52.30(2C, piperazine); EI-MS,  $m/z$ : 386.50  $[M+H]^+$ .

*4-(2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-hydroxyethyl)benzotrile (4e)*. Off white solid, Yield: 85%; M.F.  $C_{22}H_{21}ClN_4O$ ; M.W. 392.88; M.P. 125–130°C;  $^1H$  NMR (DMSO- $d_6$ , 400MHz):  $\delta$  8.70 (d,  $J = 4.8$  Hz, 1H), 8.02–7.97 (m, 2H), 7.81(d,  $J = 8.0$  Hz, 2H), 7.60–7.53 (m, 3H), 7.00(d,  $J = 5.2$  Hz, 1H), 5.41 (s, 1H), 4.86 (s, 1H), 3.16 (s, 4H, -CH<sub>2</sub> piperazine), 2.79 (s, 4H, -CH<sub>2</sub> piperazine), 2.66–2.61 (m, 1H), 2.57–2.49 (m, 1H);  $^{13}C$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.63(1C), 150.89(1C), 149.03(1C), 146.34(1C), 133.99(1C), 131.29(2C), 127.87(2C), 125.49(1C), 125.31(1C), 123.98(1C), 120.80(1C), 117.82(1C), 110.35(1C), 108.07(1C), 67.23(1C, CHOH), 64.63(1C), 52.21 (2C, piperazine), 51.14(1C, piperazine); EI-MS,  $m/z$ : 393.14  $[M+H]^+$ .

*2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-(2,4-dichlorophenyl)ethanol(4f)*. Gummy, Yield: 80%; M.F.  $C_{21}H_{20}Cl_3N_3O$ ; M.W. 436.76; M.P. 115–120°C;  $^1H$  NMR (DMSO- $d_6$ , 400MHz):  $^1H$  NMR (DMSO- $d_6$ , 400MHz):  $\delta$  8.70 (d,  $J = 4.80$ Hz, 1H), 8.03 (d,  $J = 8.80$  Hz, 1H), 7.97 (s, 1H), 7.63 (d,  $J = 8.40$  Hz, 1H), 7.56–7.54 (m, 2H), 7.47–7.45 (m, 1H), 7.01 (d,  $J = 4.80$  Hz, 1H), 5.49 (s, 1H), 5.12 (s, 1H), 3.18 (s, 4H, -CH<sub>2</sub> piperazine), 2.81 (s, 4H, -CH<sub>2</sub> piperazine), 2.56 (s, 2H);  $^{13}C$  NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  155.74(1C), 150.86(1C), 148.99(1C), 136.84(1C), 133.97(1C), 132.50(1C), 131.10(1C), 128.00(1C), 127.80(1C), 127.23(1C), 126.54(1C), 125.26(1C), 124.06(1C), 120.8(1C), 108.02(1C), 64.62(1C,CHOH), 62.78(1C), 52.21(2C,piperazine), 51.15(2C,piperazine); EI-MS,  $m/z$ : 436.30  $[M]^+$ .

#### 2.4. General procedure for synthesizing compounds (5a–5f).

To a solution of hydroxy compound (4a–4f) (1.0 mol eq.) in dichloromethane (10v) was added Diethylaminosulfur trifluoride (DAST) (2.0 mol eq.) dropwise at -5 to 0°C (exothermicity observed on addition of DAST). The reaction mass was stirred at the same temperature for 2–4h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane (1:1) as a solvent system and seen in a UV light (254nm). After the reaction is completed, as confirmed by TLC, the reaction mass is quenched with methanol (1v), and the temperature is maintained at 0°C. Poured the reaction mixture into DM water (10v) and separated the layers. The Dichloromethane layer was then washed with 8% NaHCO<sub>3</sub> solution (5v) and then with water (5v). The Dichloromethane layer was distilled off under reduced pressure at 40°–45°C to obtain an oily crude fluorinated product (5a–5f). Crude fluorinated product was then purified by column chromatography using 230–400 mesh silica gel and 50–70% Ethyl acetate/ hexane as mobile phase. The pure fractions were collected and distilled under vacuum at 45°–50°C to obtain desired material (Yield: 60–65%).

*7-chloro-4-(4-(2-fluoro-2-phenylethyl)piperazin-1-yl)quinoline (5a)*. Gummy, Yield: 65%; M.F.  $C_{21}H_{21}ClFN_3$ ; M.W. 369.86;  $^1H$  NMR (DMSO, 400MHz):  $\delta$  8.71 (d,  $J = 5.2$  Hz, 1H), 8.02 (d,  $J = 8.8$  Hz, 1H), 7.98 (s, 1H), 7.57–7.54 (m, 1H), 7.43–7.38 (m, 5H), 7.02 (d,  $J = 4.8$  Hz, 1H), 5.88–5.75 (dd, 1H, -CH coupled with fluoro), 3.20 (s, 4H, -CH<sub>2</sub> piperazine), 3.05–2.95 (m, 1H), 2.85 (s, 4H, -CH<sub>2</sub> piperazine), 2.72–2.49 (m, 1H);  $^{13}C$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.95(1C), 150.84(1C), 148.95(1C), 137.52 (d,  $J = 19.8$  Hz, (1C)), 133.92(1C), 127.72(3C), 125.16(1C), 124.4 (d,  $J = 6.8$  Hz, (1C)), 124.16(1C), 120.8(1C), 107.97(1C), 91.7 (d,  $^1J_{CF} = 172.7$  Hz, (1C, CHF)), 63.42 (d,  $^2J_{CF} = 23.1$  Hz, (1C)), 52.44(2C,piperazine), 51.09 (2C,piperazine); EI-MS,  $m/z$ : 370.26  $[M+H]^+$ .

7-chloro-4-(4-(2-fluoro-2-(4-methoxyphenyl)ethyl)piperazin-1-yl)quinoline (5b). Gummy, Yield: 62%, M.F. C<sub>22</sub>H<sub>23</sub>ClFN<sub>3</sub>O; M.W. 399.88; <sup>1</sup>H NMR (DMSO, 400MHz): δ 8.71 (d, J=4.92, 1H), 8.03 (d, J=8.76, 1H), 7.97 (s, 1H), 7.56 (d, J=8.76, 1H), 7.38 (d, J=8.52, 2H), 7.02 (d, J=4.96, 1H), 6.97 (d, J=8.48 Hz, 2H), 5.80–5.65 (dd, 1H, -CH coupled with fluoro), 3.76 (s, 3H), 3.19 (s, 4H, CH<sub>2</sub> piperazine), 3.03–2.99 (m, 1H), 2.83 (s, 4H, CH<sub>2</sub> piperazine), 2.78–2.66 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 158.80 (1C), 155.91(1C), 150.87(1C), 148.99(1C), 133.85(1C), 129.65 (d, J = 20.2 Hz, (1C)), 127.74(1C), 126.15 (d, J = 6.1 Hz, (1C)), 125.10(1C), 124.18(1C), 120.84(1C), 112.91(2C), 107.96(1C), 91.54 (d, <sup>1</sup>J<sub>CF</sub> = 171.3 Hz, (1C,CHF), 63.18 (d, <sup>2</sup>J<sub>CF</sub> = 23.9 Hz, (1C)), 54.28(1C, OCH<sub>3</sub>), 52.44 (2C, piperazine), 51.09 (2C, piperazine); EI-MS, m/z: 400.00 [M]<sup>+</sup>.

7-chloro-4-(4-(2-(4-chlorophenyl)-2-fluoroethyl)piperazin-1-yl)quinoline (5c). Gummy, Yield: 60%; M.F. C<sub>21</sub>H<sub>20</sub>Cl<sub>2</sub>FN<sub>3</sub>; M.W. 404.30; <sup>1</sup>H NMR (DMSO, 400MHz): δ 8.71 (d, J=4.96, 1H), 8.03 (d, J=9.04, 1H), 7.98 (s, 1H), 7.68–7.65 (m, 1H), 7.57–7.45 (m, 4H), 7.02 (d, J=5.00 Hz, 1H), 5.90–5.77 (dd, 1H, -CH coupled with fluoro), 3.19 (s, 4H), 3.02–2.93 (m, 1H), 2.82 (s, 4H), 2.72–2.69 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 157.03(1C), 151.91(1C), 150.02(1C), 137.21 (d, J = 20.4 Hz, (1C)), 135.03(1C), 134.46(1C), 128.84 (d, J = 2.4 Hz, (2C)), 127.05 (d, J = 6.8 Hz, (1C)), 126.30(1C), 125.26(1C), 121.92(1C), 109.07(1C), 92.24 (d, <sup>1</sup>J<sub>CF</sub> = 173.6 Hz, (1C, CHF)), 64.28 (d, <sup>2</sup>J<sub>CF</sub> = 23.1 Hz, (1C)), 53.58(2C, piperazine), 52.20, (2C, piperazine); EI-MS, m/z: 404 [M]<sup>+</sup>.

7-chloro-4-(4-(2-fluoro-2-(4-fluorophenyl)ethyl)piperazin-1-yl)quinoline (5d). Off white solid, Yield: 65 %; M.F. C<sub>21</sub>H<sub>20</sub>ClF<sub>2</sub>N<sub>3</sub>; M.W. 387.85; <sup>1</sup>H NMR (DMSO, 400MHz): δ 8.71 (d, J=5.20 Hz, 1H), 8.03 (d, J=8.80 Hz, 1H), 7.98 (d, J=2.00 Hz, 1H), 7.57–7.54 (m, 1H), 7.51–7.48 (m, 2H), 7.29 (t, J=15.6 Hz, 2H), 7.04 (d, J=8.40 Hz, 1H), 5.90–5.75 (dd, 1H, -CH coupled with fluoro), 3.19 (s, 4H, -CH<sub>2</sub> piperazine), 3.07–2.97 (m, 1H), 2.86–2.80 (m, 4H, -CH<sub>2</sub> piperazine), 2.78–2.67 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 162.82 (d, J= 246.2 Hz, 1C), 156.99(1C), 152.00(2C), 150.13(1C), 135.01(1C), 134.51 (dd, J = 20.2 Hz, J = 2.7 Hz, (1C)), 128.91(1C), 127.53(1C), 126.27(1C), 125.25(1C), 121.95(1C), 115.63 (d, J = 21.6 Hz, (1C)), 109.09(2C), 92.33 (d, <sup>1</sup>J<sub>CF</sub> = 173.0 Hz, (1C, CHF), 64.37 (d, <sup>2</sup>J<sub>CF</sub> = 23.3 Hz, (1C)), 53.60(2C, piperazine), 52.21(2C, piperazine); EI-MS, m/z: 388.50 [M+H]<sup>+</sup>.

4-(2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)-1-fluoroethyl)benzotrile (5e). Gummy, Yield: 60%; M.F. C<sub>22</sub>H<sub>20</sub>ClFN<sub>4</sub>; M.W. 394.87; <sup>1</sup>H NMR (DMSO, 400MHz): δ 8.71 (d, J=5.2 Hz, 1H), 8.10 (d, J= 14Hz, 1H), 8.0 (s, 1H), 7.91 (d, J<sub>1</sub>=8.0 Hz, 2H), 7.64 (d, J= 8.0 Hz, 2H), 7.57 (d, J=8.8 Hz, 1H), 7.02 (d, J=5.2 Hz, 1H) 6.01–5.88 (dd, 1H, -CH coupled with fluoro), 3.18 (s, 4H, -CH<sub>2</sub> piperazine), 3.04–2.94 (m, 1H), 2.84 (s, 4H, -CH<sub>2</sub> piperazine), 2.82–2.78 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.79 (1C), 150.85(1C), 148.98(1C), 142.79 (d, J = 20.0 Hz, (1C)), 133.94 (1C), 131.34(2C), 127.79(1C), 125.20(1C), 125.05 (d, J = 7.7Hz, (1C)), 124.08, (2C), 120.81(1C), 117.43(1C), 111.28(1C), 108.00(1C), 90.86 (d, <sup>1</sup>J<sub>CF</sub> = 175.7 Hz, 1C,CHF), 62.91 (d, <sup>2</sup>J<sub>CF</sub> = 22.7 Hz, (1C)), 52.49 (2C, piperazine), 51.07(2C, piperazine); EI-MS, m/z: 395.28 [M+H]<sup>+</sup>.

7-chloro-4-(4-(2-(2,4-dichlorophenyl)-2-fluoroethyl)piperazin-1-yl)quinoline (5f). Oily mass, Yield: 63%; M.F. C<sub>21</sub>H<sub>19</sub>Cl<sub>3</sub>FN<sub>3</sub>; M.W. 438.75; <sup>1</sup>H NMR (DMSO, 400MHz): δ 8.71 (d, J=4.80 Hz, 1H), 8.04 (d, J=8.80 Hz, 1H), 7.98 (s, 1H), 7.70 (s, 1H), 7.60–7.53 (m, 3H), 7.02 (d, J=5.20 Hz, 1H), 6.12–5.98 (dd, 1H, -CH coupled with fluoro), 3.20 (s, 4H, -CH<sub>2</sub> piperazine), 3.03–2.73 (m, 6H, -CH<sub>2</sub> piperazine); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.91(1C), 150.87(1C), 148.99(1C), 133.91 (d, J = 16.4 Hz, (1C)), 133.73 (d, J = 15.5 Hz, (1C)), 130.44 (d, J = 5.7 Hz, (1C)), 128.21(1C), 127.77(1C), 126.72 (d, <sup>1</sup>J<sub>CF</sub> = 10.4 Hz, (1C)), 126.55(1C), 125.15(1C),

124.15(1C), 120.81(1C), 107.99(1C), 88.20 (d,  $J = 175.1$  Hz, (1C,CHF)), 61.71(d,  $^2J_{CF} = 22.6$  Hz, (1C)), 52.28(2C,piperazine), 51.08(2C,piperazine); EI-MS,  $m/z$ : 438.30 [M]<sup>+</sup>.

### 2.5. Screening of antimalarial activity of synthesized compounds.

All the synthesized compounds (3a–3f, 4a–4f & 5a–5f) were evaluated for their antimalarial activity. In accordance with Rieckmann *et al.*'s Microassay Protocol, *in vitro* antimalarial assays were performed in 96-well microtiter plates with slight modifications [38–41]. The cultures of *plasmodium falciparum* strain were maintained in RPMI 1640 medium supplemented with 25mM HEPES, 1% D-glucose, 0.23% NaHCO<sub>3</sub>, and 10% heat-inactivated human serum. The asynchronous *plasmodium falciparum* parasite was treated with 5% sorbitol, synchronized, and only ring phase parasitic cells were obtained. For carrying out the assay, the initial 3% hematocriting stage parasitemia was determined by Jaswant Singh Bhattacharya (JSB) staining in the total volume of 200  $\mu$ L RPMI1640 medium to be 0.8% to 1.5% to evaluate the percentage of parasitemia (rings) and was uniformly maintained with 50% red blood cells (O<sup>+</sup>). Prepare a 5 mg/mL stock solution of each test sample in DMSO and then dilute it with a culture medium. Add sample diluted in 20  $\mu$ L volume to the test wells to obtain the final concentration (diluted five times), ranging from 0.4  $\mu$ g/mL to 100  $\mu$ g/mL in duplicate well containing parasitic cell preparation. The culture plate is incubated at 37°C in a candle jar. Thin blood smears from each well were produced and stained with JSB stain after 36 to 40 hours of incubation. [42–43]. Observe the slides under a microscope to record the maturation of ring-stage parasites in trophozoites and schizonts in the presence of different concentrations of test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC). Chloroquine was used as the reference drug. The mean number of rings, trophozoites, and schizonts recorded per 100 parasites from duplicate wells after incubation for 38 hours, and percent maturation inhibition with respect to the control group.

## 3. Results and Discussion

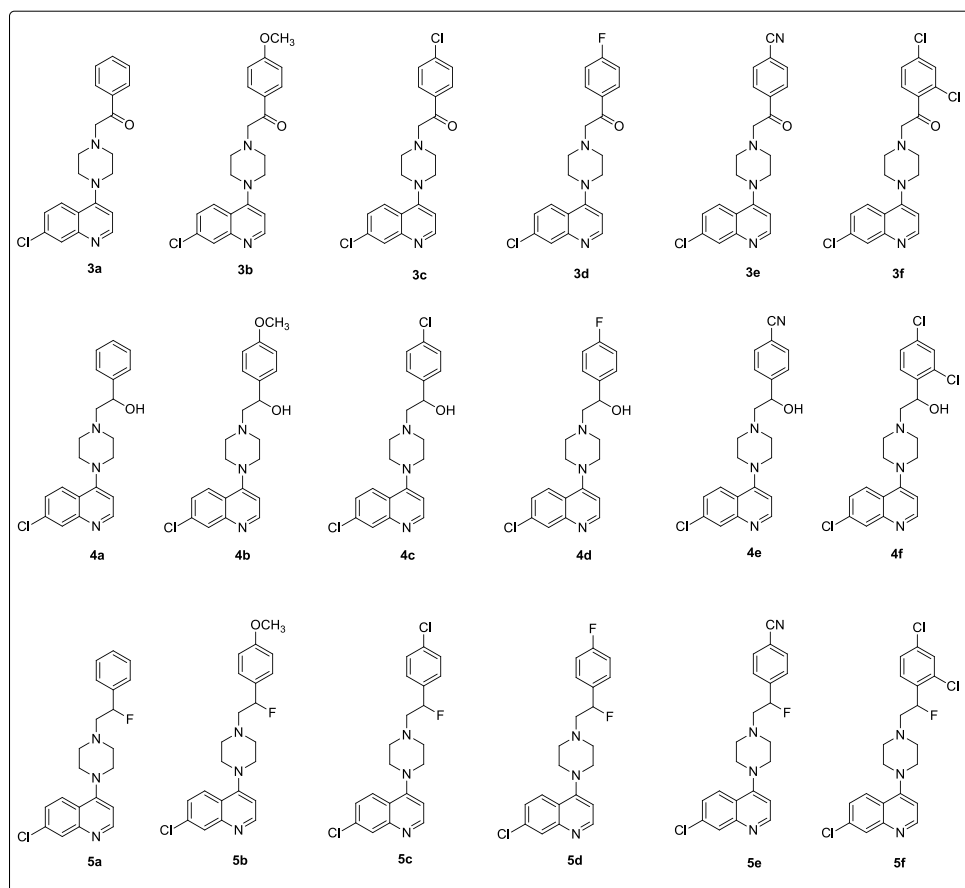
### 3.1. Chemistry.

Target compound synthesis is designed over four steps: Firstly, the addition of piperazine to 4,7-dichloroquinoline. Secondly, nucleophilic addition of substituted phenacyl bromides to 7-chloro-4-(piperazin-1-yl)quinoline (2) to obtain keto derivatives (3a–3f). Thirdly, reduction of keto analogs (3a–3f) with sodium borohydride in Ethanol/ THF to obtain hydroxyl derivatives (4a–4f) and finally fluorination using Diethylaminosulfur trifluoride (DAST) to obtain fluoro analogs (5a–5f). Structures of the synthesized compounds are shown in (Figure 4). All the synthesized compounds were characterized by analytical tools such as <sup>1</sup>H NMR, <sup>13</sup>C NMR, and EIMS analysis. Carbon (<sup>13</sup>C) and fluorine (<sup>19</sup>F) interaction in <sup>13</sup>C NMR spectra during fluorination of hydroxy derivatives (4a–4f) to consecutive fluoro derivatives (5a–5f) can be seen. <sup>19</sup>F is a highly abundant isotope of fluorine having spin 1/2. Similar to two neighboring hydrogen nuclei coupling patterns in <sup>1</sup>H NMR spectrum, fluorine can couple with carbon nuclei (<sup>13</sup>C, also having spin 1/2).

<sup>13</sup>C NMR pulse sequence without C-F decoupling shows C-F splitting in carbon spectrum. -CH-OH carbon peak of **4a** at  $\delta$ 67.85 shifts downfield to  $\delta$ 99.62 ( $\alpha$  carbon of -CH-F) in **5a** with peak splitting due to coupling with a highly electronegative fluorine atom,



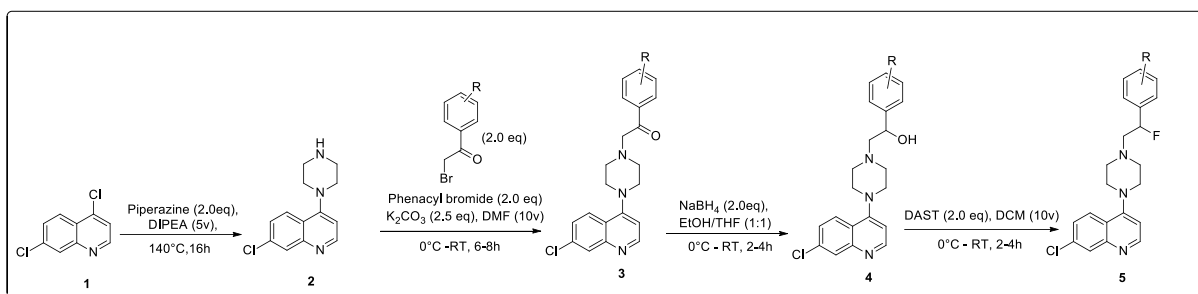
showing high coupling constant  $^1J_{CF} = 172.7$ .  $\beta$  carbon is also coupled with fluorine with a lower coupling constant  $^2J_{CF} = 23.1$ .



**Figure 4.** 7-chloro-4-(4-(2-(oxo, hydroxyl & fluoro-2-(4-phenyl)ethyl)piperazin-1-yl)quinoline derivatives.

Shifting of  $\beta$  carbon peak ( $-\text{CH}_2-\text{CH}-\text{OH}$ ) from  $\delta 65.15$  in compound **4a** to  $\delta 63.53$  in **5a** is observed. Similarly, in compound **4b** to **5b**,  $\alpha$  carbon peak at  $\delta 68.57$  split and shifts downfield to  $92.40$  (d,  $^1J_{CF}=173.6$ ) and  $\beta$  carbon peak at  $\delta 66.17$  splits and shifts to  $63.30$  (d,  $^2J_{CF}=23.1$ ). Compound **4c** to **5c**  $\alpha$  carbon peak at  $\delta 68.34$  split and shifts downfield to  $93.11$  (d,  $^1J_{CF}=173.6$ ) and  $\beta$  carbon peak at  $\delta 66.11$  split and shifts to  $64.39$  (d,  $^2J_{CF}=23.1$ ). Compound **4d** to **5d**  $\alpha$  carbon peak at  $\delta 68.38$  split and shifts downfield to  $93.20$  (d,  $^1J_{CF}=173.0$ ) and  $\beta$  carbon peak at  $\delta 66.26$  split and shifts to  $64.49$  (d,  $^2J_{CF}=23.3$ ). Compound **4e** to **5e**  $\alpha$  carbon peak at  $\delta 67.23$  split and shifts downfield to  $91.74$  (d,  $^1J_{CF}=175.7$ ) and  $\beta$  carbon peak at  $\delta 64.63$  split and shifts to  $63.02$  (d,  $^2J_{CF}=22.7$ ). Compound **4f** to **5f**  $\alpha$  carbon peak at  $\delta 64.62$  split and shifts downfield to  $89.07$  (d,  $^1J_{CF}=175.1$ ) and  $\beta$  carbon peak at  $\delta 62.78$  split and shifts to  $61.82$  (d,  $^2J_{CF}=22.6$ ).

The optimized conditions for the synthesis involve, firstly, nucleophilic addition of 4,7-dichloroquinoline with piperazine to obtain 7-chloro-4-(piperazin-1-yl)quinoline in DIPEA at  $110^\circ\text{C}$  for 16h. Secondly, nucleophilic substitution reaction of heteroaryl piperazines with substituted phenacyl bromides in DMF at  $0^\circ$ – $25^\circ\text{C}$  for 6–8h. Thirdly reduction of keto compounds in Ethanol/ THF (1:1) with  $\text{NaBH}_4$  at  $0^\circ$ – $25^\circ\text{C}$  for 4–6h and finally, fluorination of hydroxy compounds in dichloromethane at  $-5^\circ$  to  $0^\circ\text{C}$  for 2–4h (Figure 5). The results are summarized in Table 1.



**Figure 5.** Synthesis of derivatives via nucleophilic substitution, reduction, and fluorination.

**Table 1.** Optimized reaction conditions.

Reaction	Solvent	Temp(°C)	Time(h)	Yield(%)
Substitution	DIPEA	110	16	51
Substitution	DMF	0 to ambient	6-8	91-95
Reduction	Ethanol/THF	0 to ambient	2-4	80-85
Fluorination	DCM	-5 to 0	2-4	60-65

### 3.2. Antimalarial activity.

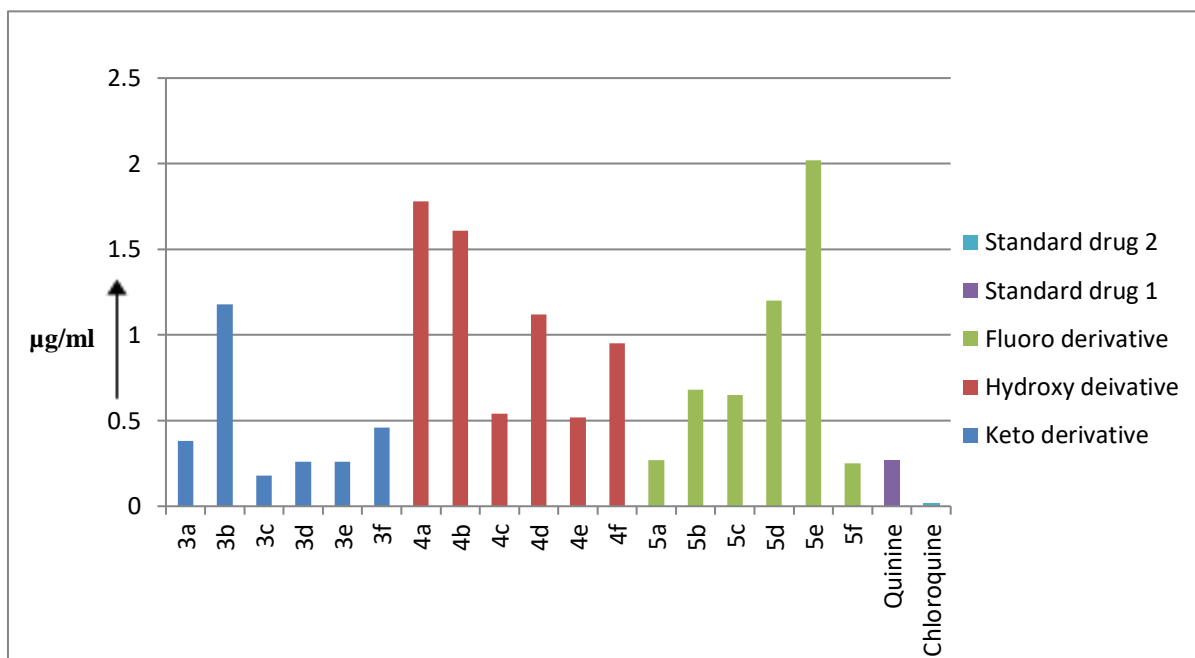
Rieckmann *et al.* assay protocol of 96 well microtitre plates was used for evaluation of the antimalarial activity of all synthesized compounds against *plasmodium falciparum* strain with minor modifications [28–31]. Chloroquine and Quinine were used as reference drugs. Minimum inhibitory concentrations (MICs) of compounds against *plasmodium falciparum* strain are summarized in Table 2.

**Table 2.** Minimum inhibitory concentration 7-chloro-4-(4-(2-(oxo, hydroxyl & fluoro-2-(4-phenyl)ethyl)piperazin-1-yl)quinoline derivatives and reference drugs against *plasmodium falciparum*.

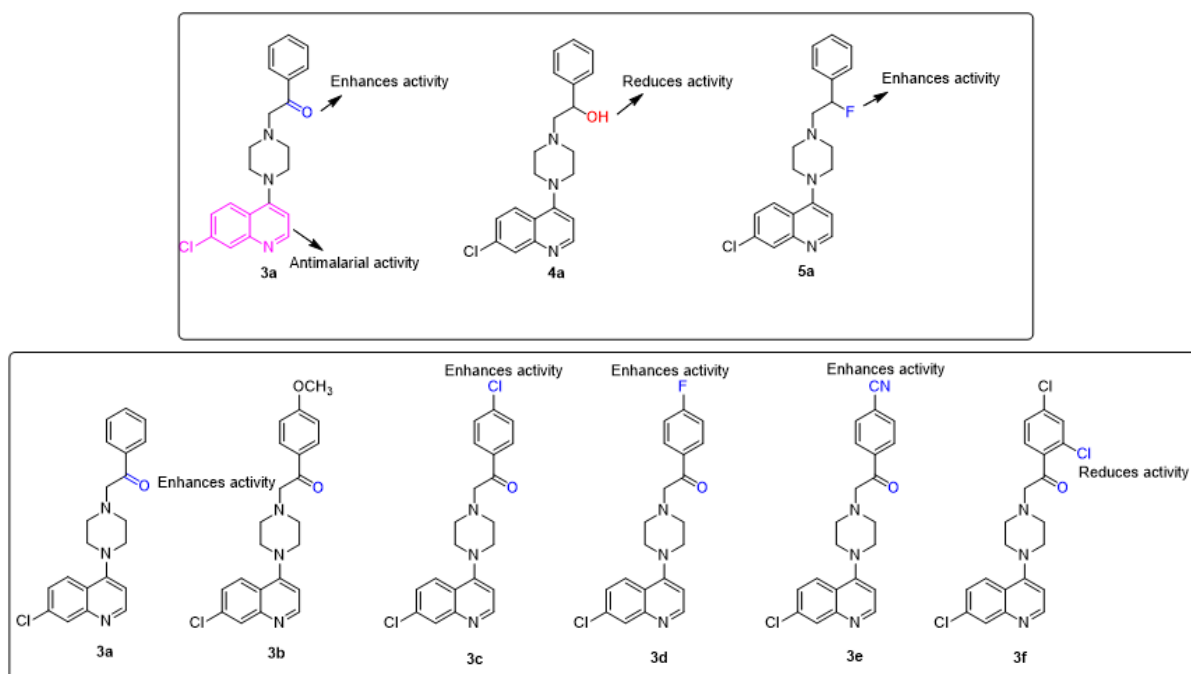
Antimalarial Activity		
Minimum Inhibitory concentration (µg/mL)		
S.NO	Compound	Mean IC50 Values (µg/mL)
1	3a	0.38
2	3b	1.18
3	3c	0.18
4	3d	0.26
5	3e	0.26
6	3f	0.46
7	4a	1.78
8	4b	1.61
9	4c	0.54
10	4d	1.12
11	4e	0.52
12	4f	0.95
13	5a	0.27
14	5b	0.68
15	5c	0.65
16	5d	1.20
17	5e	2.02
18	5f	0.25
19	Quinine	0.26
20	Chloroquine	0.02

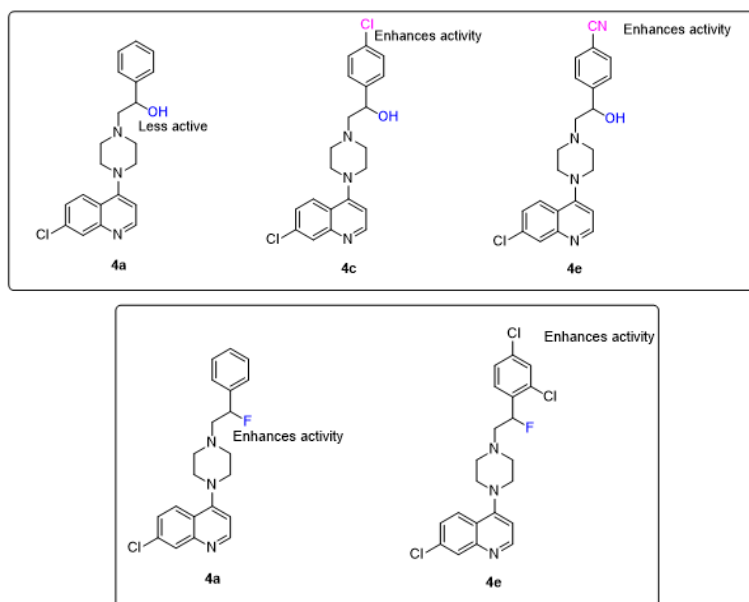
Compounds (**3a–3f**, **4a–4f**, and **5a–5f**) were primarily screened for their *in vitro* antimalarial activity. The antimalarial Chloroquine and Quinine were taken as positive controls. Compound **3c** having a 4-Cl group on the phenyl ring was found to be more potent (MIC: 0.18 µg/mL) against *plasmodium falciparum* strain as compared to the standard drug (Quinine). When the reduction of **3c** (keto group) was made to **4c** (hydroxy group), the decline in the activity was observed (MIC: 0.54 µg/mL). A similar trend in activity reduction was observed when fluorination of **4c** (hydroxy group) to **5c** (fluoro group) was carried out. This

concluded that the keto group resulted in enhanced activity, while the presence of the hydroxyl group resulted in lower activity which further decreases when the fluoro group is present. A similar trend was observed when the phenyl ring was substituted with the fluoro and cyano groups. Compound **3d** (MIC: 0.26  $\mu\text{g/mL}$ ) was found to be equipotent to the standard drug, but however, its activity reduces upon reduction (compound **4d**, MIC: 1.12  $\mu\text{g/mL}$ ) and then fluorination (compound **5d**, MIC: 1.20  $\mu\text{g/mL}$ ).



**Figure 6.** Antimalarial activity 7-chloro-4-(4-(2-(oxo, hydroxyl & fluoro-2-(4-phenyl)ethyl)piperazin-1-yl)quinoline derivatives and reference drugs against *Plasmodium falciparum*.





**Figure 7.** Structure-activity relationship for antimalarial activity.

Phenyl substituted cyano group compound **3e** (keto group) showed MIC: 0.26  $\mu\text{g/ml}$ , whose activity reduces upon reduction (compound **4e**, MIC: 0.52  $\mu\text{g/mL}$ ) and then fluorination (compound **5e**, MIC: 2.02  $\mu\text{g/mL}$ ). In contrast it was observed that fluorination of compound **4a** (MIC: 1.78  $\mu\text{g/mL}$ ) resulted in enhanced activity of compound **5a** (MIC: 0.27  $\mu\text{g/mL}$ ) and similar trend was observed with fluorination of compound **4f** (MIC: 0.95  $\mu\text{g/mL}$ ) to compound **5f** (MIC: 0.25  $\mu\text{g/mL}$ ). The comparative activity chart and structure-activity relationship of the synthesized molecules against the reference drug are shown in Figure 6 and Figure 7, respectively.

#### 4. Conclusions

18 compounds in a series of 7-chloro-4-(4-(2-(oxo, hydroxyl & fluoro-2-(4-phenyl) ethyl) piperazin-1-yl)quinoline derivatives were synthesized. Most of the synthetic compounds showed inhibitory activity against *Plasmodium falciparum* strain. Compound **3c** was found to be the most active compound having MIC 0.18  $\mu\text{g/ml}$ . On the other hand, **3d**, **3e**, **5a**, and **5f** were found to be equipotent (MIC 0.26  $\mu\text{g/ mL}$ ) to the standard drug. Therefore these compounds can act as a lead compound for further structural optimization and development as a potential antimalarial drug.

#### Funding

This research received no external funding.

#### Acknowledgments

The authors acknowledge Guru Nanak Dev University, Amritsar for analytical support, and the NorthCap University for providing the facilities for research work and literature survey.

#### Conflicts of Interest

The authors declare no conflict of interest.

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