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Design and synthesis of new quinoline hybrid derivatives and their antimicrobial, antimalarial and antitubercular activities

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All the molecules have been designed on the basis of previously reported active pharmacophores *via* molecular hybridization. A convenient protocol for the preparation of *N*-((2-(piperazin-1-yl) quinolin-3-yl)methyl)aniline derivatives *via* mutli-step synthesis has been described. Spectral analysis using Mass, ^{1}H and ^{13}C NMR spectral techniques have been studied in order to confirm the structure of synthesized end molecules. All synthesized compounds have been screened for *in vitro* antimicrobial, antimalarial and antitubercular activities. Structural activity relationship study (SAR) have also been discussed. Interestingly, target molecules are found to show good to excellent antibacterial, antifungal and antimalarial potency.

Keywords: Molecular hybridization, pharmacophore, quinoline, structural activity relationship (SAR), antimicrobial activity, antimalarial activity, antitubercular activity

Heterocycles comprising a nitrogen atom have interesting medicinal and pharmaceutical properties[1,2]. Among them, quinoline derivatives are exceptional nitrogen-containing heterocycles which concerned specific attention having superior place as building blocks of various pharmaceutical agents, natural products and biological active molecules[3-5].

Quinoline is a significant nucleus which has attracted the attention of medicinal chemists due to its variable pharmacological activities. Easy functionalization of various ring positions of quinoline makes it an attractive synthetic building block for design and synthesis of new drugs. Additionally, quinolines are considered as an interesting group of compounds, many of which have widespread pharmacological actions such as antitubercular[6-9], anti-microbial[10-13], antihypertensive[14,15], anti-inflammatory[16-19], anticancer[20,21], anti-convulsant[22-23], and antioxidant[24-26] activities. Quinoline scaffolds get much attention due to their miscellaneous therapeutic and pharmacological properties such as antiatherosclerotic, vasodilator, geroprotective, bronchodilator and hepatoprotective activity[27-29]. Numerous strategies have been considered for the preparation of quinoline derivatives like Skraup, Meth-Cohn, Conrad-Limpach, Combes, Doebner-von Miller, and Pfitzinger syntheses. Out of them, Meth-Cohn protocol for the synthesis of substituted 2-chloro-3-formylquinolines get much attention in recent years[30].

In recent years, the expansion of antimicrobial agents becomes one of the leading areas of antibacterial research, because of their resistance to the existing antibacterial and antifungal drugs[31-33]. Thus the development of new and novel antimicrobial agents are highly essential to survive this situation. This is the area why it seems crucial in order to examine for novel antimicrobial molecules with new mechanisms of action, to overcome antimicrobial resistance[34].

Similarly, malaria is an infectious disease caused by a parasite (Plasmodium) that occurs in tropical and subtropical regions. The World Health Organization (WHO) estimates that half of the world population is at risk of malarial infection[35]. Since the discovery of the natural product quinine, many compounds with a quinoline scaffold have displayed good antimalarial activity, leading to the development of effective antimalarial agents, including chloroquine, amodiaquine, pamaquine and mefloquine (Figure 1)[36-38]. Nowadays, these drugs are falling to resistance in some parts of the world. The most potent Artemisinin and its derivatives, widely used in combination therapies for curing malaria worldwide are also now falling to resistance.

Furthermore, Tuberculosis (TB) is one of the most deadly diseases that kills over one million people each

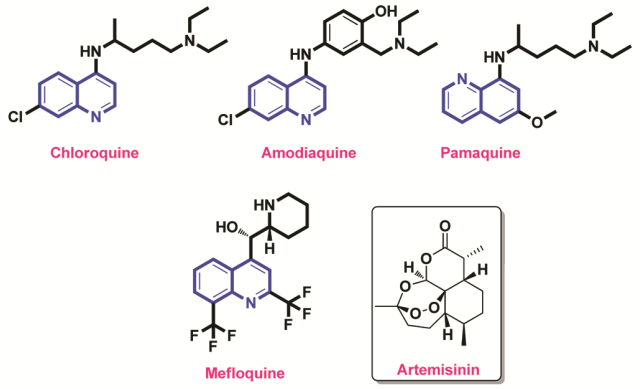


Figure 1 — Quinoline based anti-malarial agents

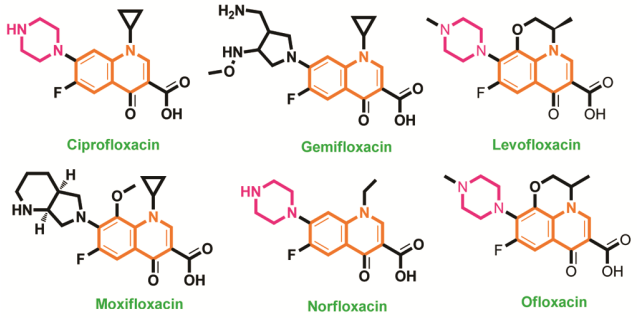


Figure 2 — Quinoline based anti-tubercular agents

year and infects one-third of the world's population. Since the last 50 years, the same long-duration, multidrug treatment plan is being followed for the treatment of tuberculosis[39]. Recently, compounds such as ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin are used for treatment of M. TB (Figure 2)[40]. Nowadays the development of resistance to these antibiotics creates a need for new therapeutic strategies to combat M. tuberculosis.

During the last decade, continues efforts in this field have led to various effective molecules succeeding to clinical trials. Due to such efforts, after 40 years, a new drug, bedaquiline (**I**), from the diarylquinoline class, with a new and innovative mechanism of action, was approved by U.S. Food and Drug Administration (US-FDA) for treatment of MDR-TB[41]. Bedaquiline exhibits excellent anti-TB potency with a minimum inhibitory concentration (MIC) of 0.1 μM. It has dynamic activity against various strains which are resistant to several of the first-line drugs[42]. Because of this, many scientist have actively worked on modifications of the quinoline scaffold, toward the development of promising anti-tuberculosis agents (Figure 3)[43-46]. In addition, newly

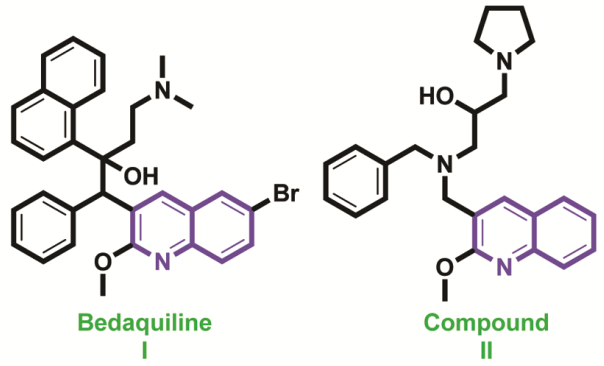


Figure 3 — Bedaquiline and their analouge as potent anti-tubercular agent

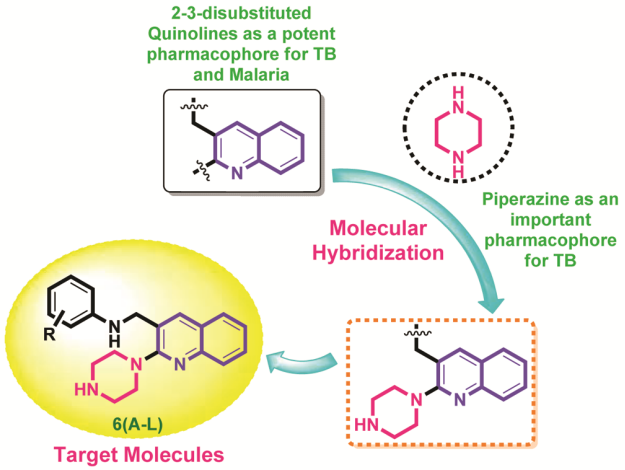


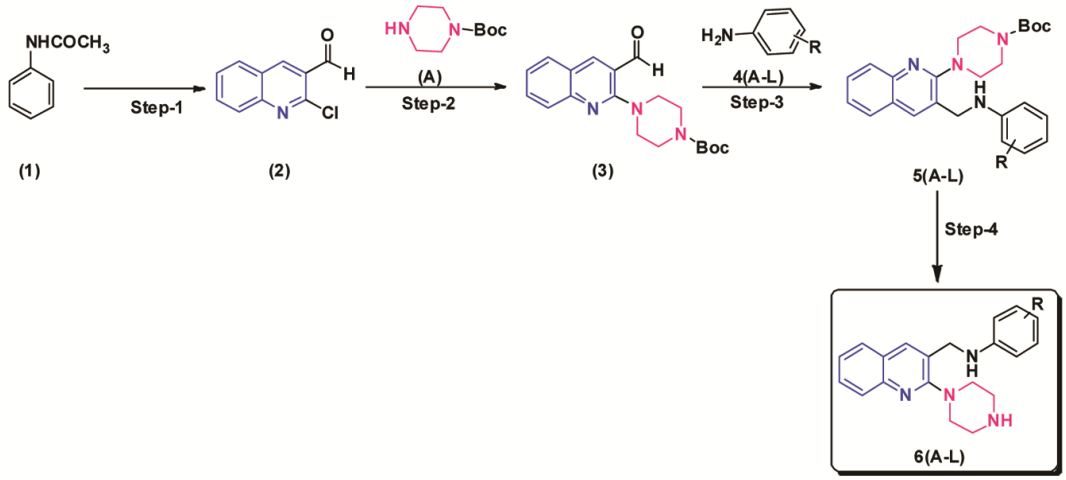
Figure 4 — Design of target molecules via molecular hybridization

approved anti-TB drug, bedaquiline (**I**) and and new bedaquiline analouge (**II**) suggest that 3-substituted quinolines tend to show promising anti-TB activity.

Furthermore, a most potent heterocyclic secondary amine called piperazine gets much attention because of its wide range of biological activities like antianginal[47,48], anticancer[49], antihistamine[50], antidepressant[51-54], antipsychotic[55], analgesic and anti-inflammatory[56].

Molecular hybridization is well known concept for the design and development of drug molecules which includes the combination of different pharmacophores of bioactive natural or synthetic substances into a single new hybrid compound with improved affinity and potency as compared to the parent drug molecules[57]. Additionally, this approach can result in compounds having different and/or dual modes of action, altered selectivity profile and decreased undesired side effects[58] (Figure 4).

Inspired by the above facts the present work proposed the design and synthesis of *N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline derivatives **6(A-L)**



Scheme I — Synthesis of quinoline hybride derivatives

achieved via reductive amination of tert-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate **(3)** with different amines **4(A-L)** followed by de-protection of N-Boc derivatives of piperazines **5(A-L)** (Scheme I).

Experimental Section

Chemistry

Materials and Methods

All reagents were used as obtained from commercial suppliers without additional purification. Melting points (mp, °C) of all the synthesized compounds were determined on an electrothermal apparatus in open capillaries and are uncorrected. The purity of synthesized compounds was checked using precoated TLC plates (Merck Keiselgel F_{254}) and visualization was attained via UV light. The FTIR spectra were recorded on IR affinity-1 FTIR (Shimadzu) spectrometer in KBr and wave numbers (ν max) are reported in cm-1 ^{1}H-NMR spectra were scanned on Bruker ADVANCE II NMR spectrometer operating at 400 MHz using DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shift (δ) values are expressed in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on WatersQuadrupole Detector (TDQ).

Procedure of synthesis of 2-chloroquinoline-3-carbaldehyde, 2

In a 3 neck RBF, $POCl_3$ (9.5eq) was added drop-wise into DMF (10V) at 0 °C. The reaction mixture was stirred for 10 min and then acetanilide was added. Heat the reaction mixture at 80 °C for 6 h. The product formation was checked by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and quenched in crushed ice with stirring. A yellow solid was observed, which was filtered off and washed with water. The yellow solid was triturated with pentane to get pure product, which was directly used for next step without further purification. Yield 78%, Yellow Solid, m.p. 202 °C, ^{1}H-NMR (400 MHZ, $CDCl_3$), 10.5 (s,1H), 8.79 (s,1H), 8.09-8.11 (d, 1H, J = 8.4 Hz), 8.00-8.02 (d, 1H, J = 8 Hz), 7.90-7.93 (t, 1H, J = 14.4 Hz), 7.66-7.70 (t, 1H, J = 14.8 Hz). MS (ESI) *m/z* for (191.01): 192.28 $(M+H)^+$.

Synthesis of *tert*-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate, 3

To a stirred solution of 2-chloroquinoline-3-carbaldehyde **(2)** (1eq) in DMF (10V), K_2CO_3 (2.5eq) was added and stirred the reaction mixture for 20 min at room temperature. After that, *tert*-butyl piperazine-1-carboxylate (2eq) was added and heated the reaction mixture at 110 °C for 5 h. The product formation was checked by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and quenched in crushed ice and extracted with ethyl acetate. The solvent was dried over sodium sulphate and evaporated under dryness to get crude product. The crude product was purified by column chromatography. The product was eluted in 10% ethyl acetate in hexane. Yield 81%, Pale Yellow Solid, m.p. 198 °C. ^{1}H-NMR (400 MHZ, $CDCl_3$) 10.21 (s,1H), 8.54 (s,1H), 7.83-7.86 (t, 1H, J = 14.8 Hz), 7.72-7.76 (t, 1H, J = 15.6 Hz), 7.41-7.44 (t, 1H, J = 15 Hz), 3.67-3.69 (t, 4H, J = 9.6 Hz), 3.46-3.49 (t, 4H, J = 9.6 Hz), 1.51 (s, 9H). MS (ESI) *m/z* for (341.17): 342.69 $(M+H)^+$.

Synthesis of *tert*-butyl 4-(3-((phenylamino)methyl) quinolin-2-yl)piperazine-1-carboxylate derivatives, 5(A-L)

To a stirred solution of Synthesis of *tert*-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate **(3)** (1eq) in methanol followed by addition of amines (1.2eq). After that catalytic amount of acetic acid was added and stirred the reaction mixture for 1 h at room temperature. The intermediate formation was checked by TLC. After that, reaction mixture was cooled at 0 °C and stirred for 10 min and then $NaCNBH_3$ (2eq) was added and stirred further at room temperature for 1 h. After completion of the reaction, the reaction mixture was then quenched in crushed ice and extracted with ethyl acetate. The crude product was purified by column chromatography.

Synthesis of *N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline derivatives, 6(A-L)

To a stirred solution of *tert*-butyl 4-(3-((phenylamino)methyl)quinolin-2-yl)piperazine-1-carboxylate derivatives **5(A-L)** in 1,4-dioxane (10V) at 0 °C, 4M HCl in 1,4-dioxane (10V) was added drop-wise and stirred the reaction mixture for 2 h at room temperature. The product formation was checked by TLC. After completion of the reaction, the reaction mixture was evaporated to dryness to get crude product and basify the reaction mixture with aq. sodium bicarbonate and extracted with DCM. Evaporate DCM layer under vacuum to get pure products **6(A-L)** after trituration with *n*-pentane.

4-Fluoro-3-methyl-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6A: Yellow solid, IR ν_{max} (KBr) cm^{-1}: 3371.68, 2947.33, 2754.44, 1643.41, 1504.53, 1449.61, 1265.35, 1033.88, 941.29, 779.27. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 9.34 (s, 1H), 8.34 (s, 1H), 7.93-7.91 (d, 1H, *J* = 8 Hz), 7.86-7.84 (d, 1H, *J* = 8 Hz), 7.71-7.67 (t, 1H, *J* = 15.2 Hz), 7.49-7.45 (t, 1H, *J* = 15.2 Hz), 7.28-7.26 (d, 1H, *J* = 8 Hz), 6.90-6.85 (t, 1H, *J* = 18.4 Hz), 6.64 (s, 1H), 6.49 (s, 1H), 4.38 (s, 1H), 3.32 (s, 4H), 2.12 (s, 4H), 1.60 (s, 3H). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 14.35, 42.44, 47.20, 115.26, 116.13, 122.75, 124.81, 125.98, 126.31, 127.58, 127.77, 129.68, 131.02, 141.32, 157.76. MS (ESI) *m/z* for (350.19): 351.5 $(M+H)^+$. Elemental Analysis: Calculated for $C_{21}H_{23}FN_4$ (350.19): C 71.98%, H 6.62%, N 15.99%; Found: C 71.95%, H 6.61%, N 15.96%.

3,4-Dimethoxy-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6B: Dark brown solid, IR ν_{max} (KBr) cm^{-1}: 3376.28, 2948.12, 2755.74, 1647.49, 1544.13, 1449.61, 1268.24, 1039.81, 945.26, 781.57. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 11.06 (s, 1H), 9.38 (s, 1H), 8.52 (s, 1H), 7.90-7.91 (d, 1H, J = 8 Hz), 7.86-7.84 (d, 1H, J = 8 Hz), 7.71-7.67 (t, 1H, J = 15.2 Hz), 7.49-7.85 (t, 2H, J = 19.6 Hz), 7.74-7.70 (t, 1H, J = 14.8 Hz), 7.52-7.49 (t, 1H, J = 18.4 Hz), 6.86-6.76 (m, 3H), 6.64 (s, 1H), 4.54 (s, 2H), 3.62 (s, 6H), 3.52 (s, 4H), 3.30 (s, 4H). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.10, 45.28, 51.40, 56.14, 97.61, 108.10, 112.82, 121.13, 122.76, 123.40, 127.35, 127.57, 129.15, 135.90, 138.21, 140.92, 148.40, 150.60, 156.62. MS (ESI) m/z for (378.21): 379.4 $(M+H)^+$. Elemental Analysis: Calculated for $C_{22}H_{26}N_4O_2$ (378.21): C 69.82%, H 6.92%, N 14.80%; Found: C 69.81%, H 6.90%, N 14.78%.

3,4-Difluoro-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl) aniline, 6C: Light brown solid, IR ν_{max} (KBr) cm^{-1}: 3340.82, 28.23.88, 2615.56, 1643.41, 1550.82, 1435.09, 1265.35, 1033.88, 941.29, 771.55. ^{1}H-NMR (400MHz,MeOD): δ_H (ppm) 8.79 (s, 1H), 8.23-8.21 (d, 1H, *J* = 8.8 Hz), 8.05-8.03 (d, 1H, *J* = 8 Hz), 7.99-7.95 (t, 1H, *J* = 15.6 Hz), 7.74-7.70 (t, 1H, *J* = 15.2 Hz), 7.09-7.02 (m, 1H), 6.67-6.62 (m, 1H), 6.50-6.48 (d, 1H, *J* = 9.2 Hz), 4.51 (s, 2H), 4.15-4.12 (t, 4H, *J* = 9.6 Hz), 3.62-3.59 (t, 4H, *J* = 9.6 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.10, 45.48, 51.20, 103.62, 114.15, 115.46, 121.35, 122.64, 123.14, 127.35, 127.72, 129.51, 135.90, 137.19, 144.82, 147.18, 148.45, 155.45. MS (ESI) *m/z* for (354.17): 355.2 $(M+H)^+$ Elemental Analysis: Calculated for $C_{20}H_{20}N_4F_2$ (354.17): C 67.78%, H 5.69%, N 15.81%; Found: C 67.75%, H 5.67%, N 15.80%.

3-Chloro-4-fluoro-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6D: Dark yellow solid, IR ν_{max} (KBr) cm^{-1}: 3356.18, 2924.22, 2725.54, 1627.19, 1545.16, 1447.68, 1269.20, 1031.83, 945.27, 788.59. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 8.79 (s, 1H), 8.22-8.20 (d, 1H, *J* = 8 Hz), 8.05-8.03 (d, 1H, *J* = 8 Hz), 7.99-7.95 (t, 1H, *J* = 15.6 Hz), 7.74-7.70 (t, 1H, *J* = 15.2 Hz), 7.09-7.02 (m, 2H), 6.67-6.62 (m, 1H), 6.50-6.48 (d, 1H, *J* = 9.2 Hz), 4.53 (s, 2H), 4.17-4.12 (t, 4H, *J* = 9.6 Hz), 3.61-3.62 (t, 4H, *J* = 9.6 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.10, 45.28, 51.40, 114.25, 115.15, 117.60, 121.32, 121.56, 122.16, 123.44, 127.34, 127.70, 129.15, 135.59, 144.55, 147.12, 148.45, 157.62. MS (ESI) *m/z* for (370.14): 371.4 $(M+H)^+$, 372.6 $(M+2H)^+$ Elemental Analysis: Calculated for $C_{20}H_{20}ClFN_4$

(370.14): C 64.77%, H 5.44%, N 15.11%; Found: C 64.75%, H 5.43%, N 15.09%.

3-Chloro-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl) aniline, 6E: Dark yellow solid, IR ν_{max} (KBr) cm^{-1}: 3326.68, 2967.52, 2747.44, 1626.25, 1535.26, 1445.52, 1261.45, 1036.23, 947.17, 778.49. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 8.79 (s, 1H), 8.22-8.20 (d, 1H, J = 8.2 Hz), 8.05-8.03 (d, 1H, J = 8 Hz), 7.99-7.95 (t, 1H, J = 15.6 Hz), 7.74-7.70 (t, 1H, J = 15.2 Hz), 7.09-7.02 (m, 2H), 6.67-6.62 (m, 2H), 6.50-6.48 (d, 1H, J = 9.2 Hz), 4.59 (s, 2H), 4.17-4.12 (t, 4H, J = 9.5 Hz), 3.61-3.62 (t, 4H, J = 9.5 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.34, 45.18, 51.30, 111.62, 113.96, 117.61, 120.74, 121.34, 122.62, 123.45, 127.31, 127.70, 129.55, 135.15, 135.90, 148.45, 149.10, 157.16. MS (ESI) *m/z* for (352.15): 353.2 $(M+H)^+$, 354.2 $(M+2H)^+$. Elemental Analysis: Calculated for $C_{20}H_{21}ClN_4$ (352.15): C 68.08%, H 6.00%, N 15.88; Found: C 68.07%, H 5.98%, N 15.86%.

2,4-Dimethoxy-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6F: Dark brown solid, IR ν_{max} (KBr) cm^{-1}: 3345.48, 2927.52, 2767.14, 1628.35, 1545.17, 1449.32, 1258.15, 1041.23, 942.18, 772.43. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 11.06 (s, 1H), 9.38 (s, 1H), 8.51 (s, 1H), 7.90-7.91 (d, 1H, J = 8 Hz), 7.86-7.84 (d, 1H, J = 8 Hz), 7.67-7.62 (t, 1H, J = 15.2 Hz), 7.49-7.85 (t, 2H, J = 19.6 Hz), 7.74-7.70 (t, 1H, J = 14.8 Hz), 7.52-7.49 (t, 1H, J = 14.8 Hz), 6.86-6.76 (m, 3H), 6.64 (s, 1H), 4.54 (s, 2H), 3.62 (s, 6H), 3.52 (s, 4H), 3.30 (s, 4H). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.32, 45.84, 51.05, 55.87, 101.29, 107.40, 115.51, 121.33, 122.65, 123.74, 127.93, 127.70, 129.50, 130.86, 135.69, 145.46, 148.42, 162.40, 156.96. MS (ESI) *m/z* for (378.21): 379.4 $(M+H)^+$ Elemental Analysis: Calculated for $C_{22}H_{26}N_4O_2$ (378.21): C 69.82%, H 6.92%, N 14.80%; Found: C 69.80%, H 6.91%, N 14.78%.

4-Chloro-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl) aniline, 6G: Brown solid, IR ν_{max} (KBr) cm^{-1}: 3346.28, 2934.12, 2727.16, 1629.15, 1539.66, 1447.50, 1262.41, 1033.43, 946.97, 776.29. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm)) 8.79 (s, 1H), 8.22-8.20 (d, 1H, J = 8.2 Hz), 8.05-8.03 (d, 1H, J = 8 Hz), 7.99-7.95 (t, 1H, J = 15.6 Hz), 7.74-7.70 (t, 1H, J = 15.2 Hz), 7.09-7.02 (m, 2H), 6.67-6.62 (m, 2H), 6.50-6.48 (d, 1H, J = 9.2 Hz), 4.59 (s, 2H), 4.17-4.12 (t, 4H, J = 9.5 Hz), 3.61-3.62 (t, 4H, J = 9.5 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.20, 45.28, 51.30, 114.19, 121.23, 122.16, 123.34, 126.41, 127.63, 127.75, 129.55, 135.29, 147.40, 148.45, 155.56. MS (ESI) *m/z* for (352.15): 353.2 $(M+H)^+$, 354.3 $(M+2H)^+$. Elemental Analysis: Calculated for $C_{20}H_{21}ClN_4$ (352.87): C 68.08%, H 6.00 %, Cl 10.05%, N 15.88%; Found: C 68.05%, H 5.98 %, Cl 10.03%, N 15.85%.

3-Methoxy-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl) aniline, 6H: Pale yellow solid, IR ν_{max} (KBr) cm^{-1}: 3345.28, 2957.12, 2777.09, 1622.21, 1534.45, 1465.52, 1271.91, 1067.45, 951.97, 777.43. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 8.79 (s, 1H), 8.22-8.20 (d, 1H, J = 8.2 Hz), 8.05-8.03 (d, 1H, J = 8 Hz), 7.99-7.95 (t, 1H, J = 15.6 Hz), 7.74-7.70 (t, 1H, J = 15.2 Hz), 7.09-7.02 (m, 2H), 6.67-6.62 (m, 2H), 6.50-6.48 (d, 1H, J = 9.2 Hz), 4.51 (s, 2H), 4.17-4.12 (t, 4H, J = 9.5 Hz), 3.83 (s, 3H), 3.61-3.62 (t, 4H, J = 9.5 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.10, 45.48, 51.20, 55.18, 105.26, 105.38, 109.42, 110.53, 121.36, 122.67, 123.48, 127.39, 127.70, 129.50, 135.19, 148.24, 148.36, 161.44, 155.66. MS (ESI) *m/z* for (348.20): 349.4 $(M+H)^+$. Elemental Analysis: Calculated for $C_{21}H_{24}N_4O$ (348.20): C 72.39%, H 6.94%, N 16.08%; Found: C 72.36%, H 6.92%, N 16.06%.

3-Methyl-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6I: Dark yellow solid, IR ν_{max} (KBr) cm^{-1}: 3345.18, 2956.22, 2767.34, 1689.25, 1536.56, 1439.72, 1264.35, 1038.14, 948.17, 781.29. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 9.34 (s, 1H), 8.34 (s, 1H), 7.93-7.91 (d, 1H, J = 8 Hz), 7.86-7.84 (d, 1H, J = 8 Hz), 7.71-7.67 (t, 1H, J = 15.2 Hz), 7.49-7.45 (t, 1H, J = 15.2 Hz), 7.28-7.26 (d, 1H, J = 8 Hz), 6.90-6.85 (t, 1H, J = 18.4 Hz), 6.64 (s, 1H), 6.49 (s, 1H), 4.38 (s, 2H), 4.22-4.16 (t, 4H, J = 9.6 Hz), 3.83 (s, 3H), 3.61-3.62 (t, 4H, J = 9.6 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 20.51, 42.45, 47.28, 123.25, 124.55, 125.45, 127.85, 128.89, 129.70, 130.20, 130.69, 137.77, 141.54, 157.62. MS (ESI) *m/z* for (332.20): 333.4 $(M+H)^+$. Elemental Analysis: Calculated for $C_{21}H_{24}N_4$ (332.20): C 75.87%, H 7.28%, N 16.85%; Found: C 75.85%, H 7.25%, N 16.82%.

4-Methyl-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl) aniline, 6J: Light yellow solid.IR ν_{max} (KBr) cm^{-1}: 3340.82, 28.23.88, 2615.56, 1643.41, 1550.82, 1435.09, 1265.35,, 1033.88, 941.29, 771.55. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 9.34 (s, 1H), 8.34 (s, 1H), 7.93-7.91 (d, 1H, J = 8 Hz), 7.86-7.84 (d, 1H, J = 8 Hz), 7.71-7.67 (t, 1H, J = 15.2 Hz), 7.52-7.48 (t, 1H, J = 15 Hz), 7.29-7.27 (d, 1H, J = 8.1 Hz), 6.91-6.86

(t, 1H, *J* = 18.2 Hz), 6.64 (s, 1H), 6.49 (s, 1H), 4.38 (s, 2H), 4.23-4.18 (t, 4H, *J* = 9.5 Hz), 3.83 (s, 3H), 3.62-3.64 (t, 4H, *J* = 9.5 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 20.50, 42.40, 47.26, 123.15, 124.50, 125.85, 127.75, 128.99, 129.75, 130.0, 130.89, 137.57, 141.44, 157.60. MS (ESI) *m/z* for (332.20): 333.2 $(M+H)^+$. Elemental Analysis: Calculated for $C_{21}H_{24}N_4$ (332.20): C 75.87%, H 7.28%, N 16.85%; Found: C 75.85%, H 7.25%, N 16.82%.

4-Methoxy-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6K: Brown solid, IR ν_{max} (KBr) cm^{-1}: 3326.68, 2967.52, 2747.44, 1626.25, 1535.26, 1445.52, 1261.45, 1036.23, 947.17, 778.49. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 9.28 (s, 1H), 8.31 (s, 1H), 7.93-7.91 (d, 1H, *J* = 8 Hz), 7.86-7.84 (d, 1H, *J* = 8 Hz), 7.70-7.69 (t, 1H, *J* = 15 Hz), 7.52-7.48 (t, 1H, *J* = 15 Hz), 7.29-7.27 (d, 1H, *J* = 8.1 Hz), 6.91-6.86 (t, 1H, *J* = 18.2 Hz), 6.62 (s, 1H), 6.46 (s, 1H), 4.31 (s, 2H), 4.22-4.17 (t, 4H, *J* = 9.4 Hz), 3.83 (s, 3H), 3.62-3.63 (t, 4H, *J* = 9.4 Hz). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 20.50, 42.40, 47.26, 51.56, 123.15, 124.50, 125.85, 127.75, 128.99, 129.75, 130.0, 130.89, 137.57, 141.44, 157.60. MS (ESI) *m/z* for (348.20): 349.3 $(M+H)^+$. Elemental Analysis: Calculated for $C_{21}H_{24}N_4O$ (348.20): C 72.39%, H 6.94%, N 16.08%; Found: C 72.36%, H 6.92%, N 16.06%.

3,5-Dimethoxy-*N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline, 6L: Brown solid, IR ν_{max} (KBr) cm^{-1}: 3376.28, 2948.12, 2755.74, 1647.49, 1544.13, 1449.61, 1268.24, 1039.81, 945.26, 781.57. ^{1}H-NMR (400MHz, DMSO-d_6): δ_H (ppm) 10.80 (s, 1H), 9.35 (s, 1H), 8.51 (s, 1H), 7.92-7.93 (d, 1H, *J* = 8.1 Hz), 7.86-7.84 (d, 1H, *J* = 8 Hz), 7.66-7.63 (t, 1H, *J* = 15.3 Hz), 7.49-7.85 (t, 2H, *J* = 19.6 Hz), 7.74-7.70 (t, 1H, *J* = 14.8 Hz), 7.52-7.49 (t, 1H, *J* = 14.8 Hz), 4.55 (s, 2H), 3.59 (s, 6H), 3.52 (s, 3H), 3.30 (s, 3H). ^{13}C-NMR (100 MHz, DMSO): δ_C (ppm) 42.10, 45.48, 51.20, 55.18, 105.26, 105.38, 109.42, 110.53, 121.36, 122.67, 123.48, 127.39, 127.70, 129.50, 135.19, 148.24, 148.36, 161.44, 155.66. MS (ESI) *m/z* for (378.21): 379.4 $(M+H)^+$. Elemental Analysis: Calculated for $C_{22}H_{26}N_4O_2$ (378.21): C 69.82%, H 6.92%, N 14.80%; Found: C 69.80%, H 6.91%, N 14.78%.

Microbiology

Antibacterial and antifungal activity

The minimal inhibitory concentration (MIC) of all synthesized compounds was determined by broth microdilution method[59]. Mueller-Hinton broth and Sabouraud's broth were used as nutrient medium to grow bacteria and fungus, respectively. Inoculum size for the test strain was adjusted to 10^6 colony-forming unit (CFU) per milliliter by comparing the turbidity. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of test organism and incubated at 37 °C for bacteria and 22 °C for fungi overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. Each test compound was diluted, obtaining 2,000 µg/mL concentration, as a stock solution. In primary screening 1000, 500, 250 and 125 µg/mL concentrations of the test compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all organisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 62.5, 25, 12.5 and 6.25 µg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

All newly synthesized compounds **6(A-L)** were examined for antimicrobial activity against two gram-positive bacterial strains (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442), two gram-negative bacterial strains (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688) as well as three fungal strains (*Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 282) using the agar dilution method. Ampicillin, Ciprofloxacin and Chloramphenicol were used as standard control drugs for antibacterial activity, whereas Nystatin and Greseofulvin were used as standard control drugs for antifungal activity.

Anti-malarial activity

A stock solution of 5 mg/mL of each of the test samples as well as standards was prepared in DMSO and subsequent dilutions were prepared with the culture medium. The diluted samples in 20 µL volume were added to the test wells so as to obtain final concentrations (at fivefold dilutions) ranging between 0.4 and 100 µg/mL in duplicate well containing parasitized cell preparation. The *in vitro* antimalarial assay was carried out in 96 well plates according to the microassay protocol of Reickmann and

co-workers with minor modifications[60]. The cultures of *P. falciparum* strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8-1.5% at 3% haematocrit in a total volume of 200 µl of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O^{+ve}). The culture plates were incubated at 37°C in a candle jar. After 36-40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of the ring stage parasites into trophozoites and schizonts in the presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC). Chloroquine and Quinine were used as the reference drugs.

Antituberculosis activity

MIC of the test compounds against M. tuberculosis $H_{37}Rv$ was determined by L. J. agar (MIC) method[61, 62] where primary 1,000, 500 and 250 µg/mL and secondary 200, 100, 50, 25, 12.5, 6.250 and 3.125 µg/mL dilutions of each test compound were added to liquid L.J medium and then media were sterilized by inspissation method. A culture of M. tuberculosis $H_{37}Rv$ growing on L.J. medium was harvested in 0.85% saline in bijou bottles. For all test compounds, first a stock solution of 2,000 µg/mL concentration was prepared in DMSO. These tubes were then incubated at 37°C for 24 h followed by streaking of M. tuberculosis $H_{37}Rv$ (5×10^4 bacilli per mL). These tubes were then incubated at 37±1°C. Growth of bacilli was seen after 12, 22 and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with M. tuberculosis H37Rv. The concentration at which no development of colonies occurred or less than 20 colonies was taken as MIC of test compound. The standard strain M. tuberculosis $H_{37}Rv$ was tested with known drug rifampicin.

Results and Discussion

Generality and optimization of the reaction

Initially, we have synthesised 2-chloroquinoline-3-carbaldehyde **(2)** from the reaction of acetanilide **(1)** with $POCl_3$ in DMF (*N.N*-dimethyl formamide) at 60°C for 5 h. After that, we have successfully prepared *tert*-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate **(3)** from the reaction of 2-chloroquinoline-3-carbaldehyde **(2)** with *tert*-butyl piperazine-1-carboxylate **(A)** in the presence of K_2CO_3 in DMF at room temperature. After successful synthesis of compound **(3)**, we have planned to develop an efficient synthesis of derivatives **5(A-L)** via reductive amination reaction. To identify the optimization reaction conditions, initially *tert*-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate **(3)** and 3-chloroaniline **(4E)** was used as the model substrates for investigating the effects of temperature, various catalyst and solvents (Table I).

Table I — Optimization of the reaction conditions for the synthesis of tert-butyl 4-(3-(((3-chlorophenyl)amino)methyl)quinolin-2-yl)piperazine-1-carboxylate (**5E**)

Entry	Catalyst	Solvent	Temp (°C)	Time	Yield[a] (%)
1	$NaCNBH_3$ and Acetic acid	Methanol	RT	1h	82
2	$NaCNBH_3$ and Acetic acid	THF	RT	1h	69
3	$NaCNBH_3$ and Acetic acid	Ethanol	RT	1h	77
4	$NaBH_4$	2,2,2-trifluoroethanol	RT	1h	52
5	$NaBH_4$ and Acetic acid	Methanol	RT	2h	67
6	$NaBH_4$ and Acetic acid	THF	RT	2h	60
7	$NaBH_4$ and Acetic acid	Ethanol	RT	2h	65
8	$NaBH(OAC)_3$ and Acetic acid	THF	RT	2h	58
9	$NaBH(OAC)_3$ and Acetic acid	Dichloroethane	RT	2h	62
10	$NaCNBH_3$ and Acetic acid	Methanol	40	1h	80
11	$NaCNBH_3$ and Acetic acid	Methanol	50	1h	76
12	$NaCNBH_3$ and Acetic acid	Methanol	60	1h	70

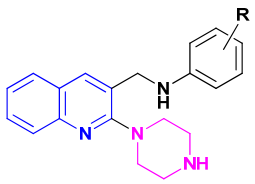
[a] = Isolated yield.
RT = Room Temperature.

In a model reaction, initially we used common reductive amination condition i.e. $NaCNBH_3$, acetic acid in methanol at room temperature, and we found that *tert*-butyl 4-(3-(((3-chlorophenyl) amino)methyl) quinolin-2-yl)piperazine-1-carboxylate **(5E)** could be produced in 82% yield within 1h (Table I, Entry 1). To improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of solvents like THF and ethanol. However, good to moderate yield was observed in THF and ethanol (Table I, Entry 2, 3). Thus, we concluded that the methanol was the best solvent for this reaction.

After that, we scrutinized different reducing agents in the same reaction conditions. Only moderate yield of compound **(5E)** was observed, when $NaBH_4$ was used as a catalyst in 2,2,2-trifluoroethanol (Table I, Entry 4). In addition $NaBH_4$ and acetic acid system was also screened in different solvents like methanol, THF, and ethanol. However, any significant change was not observed in product yield, only moderate yields were observed in all cases (Table I, Entry 5-7). Moreover, $NaBH(OAC)_3$ and acetic acid system was also tested by using THF and dichloroethane (DCE) as a solvent for this reaction. However, they were not found to be efficient as like $NaCNBH_3$ and acetic acid (Table I, entry 8, 9). Thus, $NaCNBH_3$ and acetic acid in methanol is optimize reaction condition. Further, increasing the temperature of the reaction from room temperature (RT) to 60 °C, which led to decreasing the product yield (Table I, entry 10-12). Thus, $NaCNBH_3$ and acetic acid in methanol at room temperature is optimized condition for this reaction. The optimal conditions found for the compound **(5E)** was successfully applied to the reactions of *tert*-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate **(3)** with different amine **4(A-L)** in the presence of $NaCNBH_3$ and acetic acid in methanol at room temperatur, which afforded corresponding *tert*-butyl 4-(3-((phenylamino)methyl)quinolin-2-yl)piperazine-1-carboxylate derivatives **5(A-L)** in good to excellent yields within 1h. We tested different aniline derivatives to assess the generalization of this protocol. The reaction proceeded smoothly and provided excellent yields in all cases. Finally, *N*-((2-(piperazin-1-yl)quinolin-3-yl)methyl)aniline derivatives **6(A-L)** were synthesised by deportation of *N*-Boc of *tert*-butyl 4-(3-((phenylamino) methyl) quinolin-2-yl)piperazine-1-carboxylate derivatives **5(A-L)** by usind 4M HCl in 1,4-dioxane (Table II). After completion of the reaction basify the reaction mixture with aq. sodium bicarbonate and extracted with DCM. Evaporate DCM layer under vacuum to get pure products **6(A-L)**.

All synthesized products were easily purified by trituration with *n*-pentane. The purity of the synthesized molecules was confirmed by TLC and elemental analysis. The structure of the final products

Table II — Preparation of various quinoline hybride piperazine derivatives **6(A-L)**



Compd Code	R	Time (h)	Yield (%)	m.p. (°C) (Lit.)
6A	3-CH_3-4-F	2	82	190-194
6B	3,4-$(OCH_3)_2$	2	78	195-199
6C	3,4-$(F)_2$	2	81	185-189
6D	3-Cl-4-F	2	76	188-192
6E	3-Cl	2	82	196-200
6F	2,4-$(OCH_3)_2$	2	81	204-208
6G	4-Cl	2	74	201-205
6H	3-OCH_3	2	80	197-199
6I	3-CH_3	2	78	194-196
6J	4-CH_3	2	75	197-198
6K	4-OCH_3	2	81	194-196
6L	3,5-$(OCH_3)_2$	2	76	203-204

[a] = Isolated yields

were well characterized by using spectral analysis (IR, Mass, ^{1}H-NMR and ^{13}C-NMR).

To check the effect of temperature on the reaction, we have carried out model reaction at different temperature under optimal reaction condition (Figure 5). The result displays that at high temperature product may degraded to lead lower yield. Best result was obtained at room temperature in terms of product yield and reaction time.

Proposed reaction mechanism

We have also defined possible reaction mechanism of formation of amide derivatives **6(A-L)** (Figure 6). In the first step, carbonyl group of aldehyde was protonized in the presence of acetic acid. This protonated intermediate react amine to form a hemiaminal species, which subsequently loses one molecule of water in to form the imine. This imine intermediate was reduced in the presence of sodium cyanoborohydride to form reductive amination product.

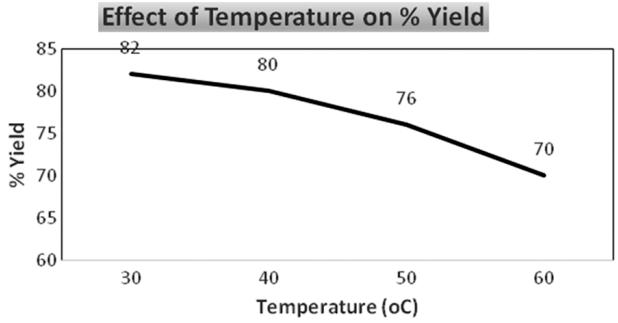


Figure 5 — Effect of temperature on conversion of **5E**

Spectroscopic characterization of quinoline hybride piperazine derivatives, 6(A-L)

IR spectra showed characteristic -NH starching peak nearer 3365 cm^{-1} is corresponding to secondary amine group and -CH starching peak nearer 2900-3000 cm^{-1} is corresponding to alkane group. In addition, characteristic N-H bending peak nearer 1650 cm^{-1} is corresponding to secondary amine group. The ^{1}H-NMR spectrum exhibited a singlet nearer 9.45 ppm, which indicated a proton of the –NH group. While peaks between 3.50 and 3.20 ppm were observed for respective piperazine protons. The ^{13}C-NMR spectrum exhibited peak nearer 155-157 ppm, which indicated C-2 carbon of quinolone nucleus, while peak nearer 45 ppm, which indicated carbon atom of CH_2-NH- group. In addition, peaks nearer 110-140 ppm indicated aromatic carbon atom. The ESI-MS spectra of compounds **6(A-L)**, show corresponding $(M+1)^+$ peak as well as $(M+2)^+$ peak. In all spectra $(M+2)^+$ peak observed due to presence of chloro group. Other spectral data of all compounds are listed in experimental section.

Pharmacology

Antimicrobial activity

In vitro antibacterial activity

All synthesized molecules were screened for their *in-vitro* antibacterial activity (Table III). From the bioassay results it is clear that, most of quinoline hybride piperazine derivatives **6(A-L)** demonstrated

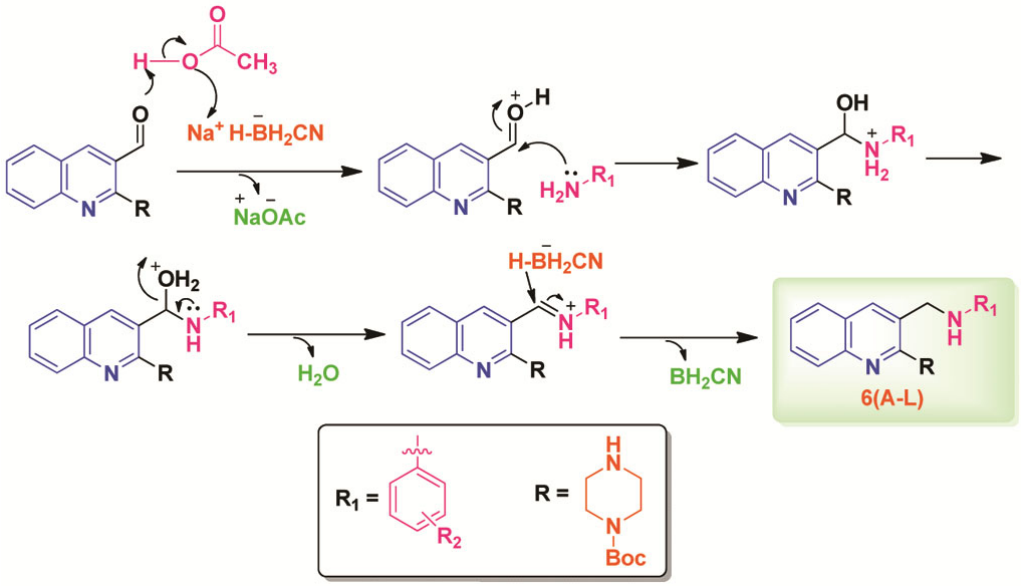


Figure 6 — Proposed reaction mechanism

Table III — Antibacterial and antifungal activity (MICs, µg/ml)

Compd	Antibacterial activity				Antifungal activity		
	Gram positive bacteria		Gram negative bacteria				
	S.A.	S.P.	E.C.	P.A.	C.A.	A.N.	A.C.
	MTCC 96	MTCC 442	MTCC 443	MTCC 1688	MTCC 227	MTCC 282	MTCC 1323
6A	100	125	125	200	500	>1000	>1000
6B	100	200	250	200	1000	1000	1000
6C	200	200	100	250	1000	1000	1000
6D	100	100	125	250	>1000	1000	1000
6E	125	125	100	100	500	500	500
6F	250	100	62.5	125	1000	1000	1000
6G	100	125	100	200	500	>1000	>1000
6H	200	100	250	100	1000	500	500
6I	125	250	62.5	100	500	1000	1000
6J	100	200	250	200	500	500	500
6K	100	250	125	100	250	500	500
6L	100	100	250	200	1000	500	500
Ampicillin	250	100	100	100	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

significant activity against the mentioned microorganisms as compared to standard drugs. In general most of the tested compounds showed more potent activity against the Gram-positive bacteria (*S. aureus*) as compared to standard drug Ampicillin (MIC 100 µg/mL), but 50% less active than Chloramphenicol (MIC 50 µg/mL) and Ciprofloxacin (MIC 50 µg/mL). Only, compound **6F** bearing two methoxy group in phenyl ring, was found to be the moderate active compound that inhibits the gram positive *S. aureus* bacterial growth at the lowest minimum inhibitory concentration (MIC) value of 250 µg/mL, which is equipotent to Ampicillin (MIC 250 µg/mL). In addition, compound **6F**, **6H**, and **6L** displayed equipotent activity with 100 µg/mL MIC against *S. pyogenus* bacteria as compared to standard drug Ampicillin, but 50% less active than Chloramphenicol (MIC 50 µg/mL) and Ciprofloxacin (MIC 50 µg/mL). Rest of compounds exhibited moderate activity against the *S. pyogenus*.

On the other hand, antibacterial activity of all synthesized compound against the two Gram-negative strains exhibited good activity. In addition, molecules **6F** and **6I** (MIC 62.5 µg/mL) displayed excellent activity against *E. coli* as compared to standard drug to Ampicillin (MIC 100 µg/mL). Furthermore, compounds **6C**, **6E**, and **6G** exhibited good activity against *E. coli* bacterial strain at the minimum inhibitory concentration (MIC) value of 100 µg/mL equivalent to Ampicillin. Moreover, analogues **6E, 6H, 6I** and **6K** (MIC 100 µg/mL) were equipotent to Ampicillin (MIC 100 µg/mL) against *P. aeruginosa*, but 50% less active than Chloramphenicol (MIC 50 µg/mL). Rest of compounds exhibited moderate activity against the *P. aeruginosa*.

In vitro antifungal activity

Concerning the antifungal activity of tested derivatives, only one strain that is *C. albicans* showed excellent sensitivity against some of the tested compounds (Table III). Antifungal activity assay displayed that among the **6(A-L)** derivatives, compounds **6A**, **6E**, **6G** and **6J** displayed moderate activity with MIC 500 µg/mL against *C. albicans* equipotent to Greseofulvin (MIC 500 µg/mL). Furthermore, only compound **6K** showed excellent activity with MIC 250 µg/mL against *C. albicans* as compared to standard drug Greseofulvin (MIC 500 µg/mL). Moreover, most of compounds showed moderate inhibitory efficiency against the *A. niger* and *A. clavatus*.

Table IV — *In vitro* antimalarial activity of compounds **6(A-L)**

Compd	Mean IC50 values (μg/mL)
6A	0.92
6B	1.09
6C	1.01
6D	0.97
6E	1.05
6F	1.03
6G	0.92
6H	0.88
6I	0.85
6J	0.96
6K	0.94
6L	1.01
Quinine	0.268
Chloroquine	0.020

Table V — *In vitro* antituberculosis activity of compounds **6(A-L)**

Compd	Mean IC50 values (μg/mL)
6A	100
6B	500
6C	100
6D	500
6E	500
6F	100
6G	50
6H	100
6I	500
6J	250
6K	1000
6L	500
Isoniazid	0.20
Rifampicin	0.25

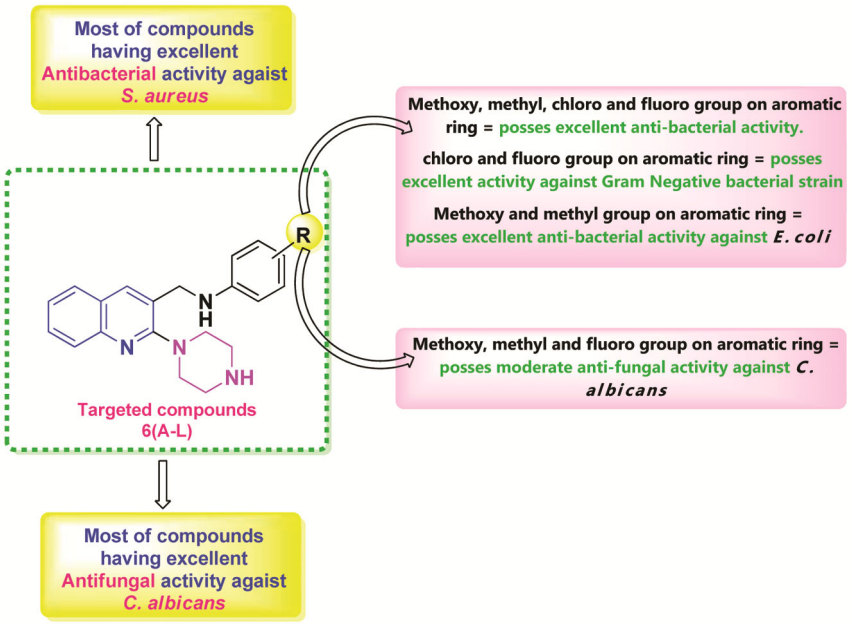


Figure 7 — Structure-activity relationship (SAR) of quinoline hybride piperazine derivatives **6(A-L)**

In vitro anti-malarial activity

All synthesized compounds **6(A-L)** were also screened for *In vitro* antimalarial activity against *Plasmodium falciparum* 3D7-chloroquine-sensitive strain. All experiments were performed in duplicate and a mean IC50 value is mentioned in Table IV. Most of compounds exhibited moderate antimalarial activity.

In vitro anti-tuberculosis activity

All synthesised derivatives **6(A-L)** were tested for their *in vitro* antituberculosis activity against Mycobacterium tuberculosis $H_{37}Rv$ strain. Isoniazid and rifampicin were used as the standard drugs. The experimental MIC values of these molecules are described in Table V. Among the screened molecules, **6G** showed the good activity (50 mg/mL). Rest of compounds exhibited moderate antitubercular efficiency.

Structure-activity relationship (SAR)

The substitution pattern of the arylamine ring at the different position was observed to affect biological activity (Figure 7). The electronic nature of the substituents led to significant effect on bioactivity. Compounds possessing -Me and -OMe group on phenyl ring led to an increase in the anti-bacterial as well as antifungal activity. In addition, the chloro and fluoro substituents on phenyl ring was found to be active against Gram negative bacterial strain.

Furthermore, most of compounds displayed excellent potency against *S. aureus* and *C. albicans*.

Conclusions

In summary, we have synthesized and characterized new quinoline hybride piperazine derivatives **6(A-L)** and screened them against some Gram-positive and Gram-negative bacteria as well as some fungi strain. From the bioassays it is clear that, the most of compounds displayed excellent potency against *S. aureus* and *C. albicans*. All derivatives also possess moderate antimalarial as well as antitubercular activity. In the present study, compounds **6E**, **6F**, **6G**, **6H**, and **6I** displayed highly potent activity against most of the tested bacteria and fungi.

Referances

1 Prajapati S M, Patel K D, Vekariya R H, Panchal S N & Patel H D, *Rsc Adv*, 4 (2014) 24463.
2 Chung P Y, Bian Z X, Pun H Y, Chan D, Chan A S C, Chui C H, Tang J C O & Lam K H, *Future Med Chem*, 7 (2015) 947.
3 Nammalwar B & Bunce R, *Molecules*, 19 (2014) 204.
4 Mphahlele M & Adeloye A, *Molecules*, 18 (2013) 15769.
5 Al-Shaalan N, *Molecules*, 12 (2007) 1080.
6 Candéa A L, Ferreira M D L, Pais K C, Cardoso L N D F, Kaiser C R, Maria das Graças M D O, Lourenço M C, Bezerra F A & de Souza M V, *Bioorg Med Chem Lett*, 19 (2009) 6272.
7 Eswaran S, Adhikari A V & Shetty N S, *Eur J Med Chem*, 44 (2009) 4637.
8 Thomas K, Adhikari A V, Telkar S, Chowdhury I H, Mahmood R, Pal N K, Row G & Sumesh E, *Eur J Med Chem*, 46 (2011) 5283.
9 Mandewale M C, Thorat B, Shelke D & Yamgar R, *Bioinorg Chem Appl*, 2015 (2015).
10 Shah N K, Shah N M, Patel M P & Patel R G, *J Serb Chem Soc*, 77 (2012) 279.
11 Wang X, Xie X, Cai Y, Yang X, Li J, Li Y, Chen W & He M, *Molecules*, 21 (2016) 340.
12 Murugavel S, Sundramoorthy S, Subashini R & Pavan P, *Struct Chem*, 29 (2018) 1677.
13 Bai X, Chen Y, Liu Z, Zhang L, Zhang T & Feng B, *Chem Biodivers*, (2019).
14 McCall J M, TenBrink R, Kamdar B V, Skaletzky L L, Perricone S C, Piper R C & Delehanty P J, *J Med Chem*, 29 (1986) 133.
15 Bülbül B, Öztürk G S, Vural M, Şimşek R, Sarioğlu Y, Linden A, Ülgen M & Şafak C, *Eur J Med Chem*, 44 (2009) 2052.
16 Khalifa N M, Al-Omar M A, El-Galil A A A & El-Reheem M A, *Biomed Res*, 28 (2017) 869.
17 Chen Y L, Zhao Y L, Lu C M, Tzeng C C & Wang J P, *Bioorg Med Chem*, 14 (2006) 4373.
18 Adams B K, Ferstl E M, Davis M C, Herold M, Kurtkaya S, Camalier R F, Hollingshead M G, Kaur G, Sausville E A & Rickles F R, *Bioorg Med Chem*, 12 (2004) 3871.
19 Rajanarendar E, Reddy M N, Krishna S R, Murthy K R, Reddy Y & Rajam M, *Eur J Med Chem*, 55 (2012) 273.
20 Jain S, Chandra V, Jain P K, Pathak K, Pathak D & Vaidya A, *Arab J Chem*, (2016).
21 Afzal O, Kumar S, Haider M R, Ali M R, Kumar R, Jaggi M & Bawa S, *Eur J Med Chem*, 97 (2015) 871.
22 Guo L J, Wei C X, Jia J H, Zhao L M & Quan Z S, *Eur J Med Chem*, 44 (2009) 954.
23 Zheng Y, Bian M, Deng X Q, Wang S B & Quan Z S, *Arch Pharm*, 346 (2013) 119.
24 Mallesha L, Kendagannaswamy B & Mohana K, *Curr Chem Lett*, 2 (2013) 119.
25 Puskullu M O, Shirinzadeh H, Nenni M, Gurer-Orhan H & Suzen S, *J Enzyme Inhib Med Chem*, 31 (2016) 121.
26 Verbanac D, Malik R, Chand M, Kushwaha K, Vashist M, Matijašić M, Stepanić V, Perić M, Paljetak H Č & Saso L, *J Enzyme Inhib Med Chem*, 31 (2016) 104.
27 Klusa V, *Drugs Future*, 20 (1995) 135.
28 Bretzel R G, Bollen C C, Maeser E & Federlin K F, *Am J Kidney Dis*, 21 (1993) S53.
29 Davis H & Davis T, *Cancer Treat Rep*, 63 (1979) 809.
30 Hamama W S, Ibrahim M E, Gooda A A & Zoorob H H, *RSC Adv*, 8 (2018) 8484.
31 Hafez H N & El-Gazzar A R B, *Acta Pharm*, 65 (2015) 215.
32 Hafez H N, Hussein H A & El-Gazzar A R B, *Eur J Med Chem*, 45 (2010) 4026.
33 Grare M, Mourer M, Fontanay S, Regnouf-de-Vains J B, Finance C & Duval R E, *J Antimicrob Chemother*, 60 (2007) 575.
34 Coleman K, *Drug Discov Today Ther Strateg*, 1 (2004) 455.
35 WHO, (2016) World Malaria Report: World Health Organization.
36 Gelb M H, *Curr Opin Chem Biol*, 11 (2007) 440.
37 Wiesner J, Ortmann R, Jomaa H & Schlitzer M, *Angew Chem Int Ed*, 42 (2003) 5274.
38 Biagini G A, O'Neill P M, Bray P G & Ward S A, *Curr Opin Pharmacol*, 5 (2005) 473.
39 Keri R S & Patil S A, *Biomed Pharmacother*, 68 (2014) 1161.
40 Xiao Z P, Li H Q, Shi L, Lv P C, Song Z C & Zhu H L, *Chem Med Chem*, 3 (2008) 1077.
41 Roberto Chiarelli L, Mori G, Esposito M, Silvia Orena B & Rosalia Pasca M, *Curr Med Chem*, 23 (2016) 3813.
42 Andries K, Verhasselt P, Guillemont J, Göhlmann H W, Neefs J M, Winkler H, Van Gestel J, Timmerman P, Zhu M & Lee E, *Science*, 307 (2005) 223.
43 Upadhayaya R S, Lahore S V, Sayyed A Y, Dixit S S, Shinde P D & Chattopadhyaya J, *Org Biomol Chem*, 8 (2010) 2180.
44 Mao J, Yuan H, Wang Y, Wan B, Pieroni M, Huang Q, Van Breemen R B, Kozikowski A P & Franzblau S G, *J Med Chem*, 52 (2009) 6966.
45 El-Sayed N S, El-Bendary E R, El-Ashry S M & El-Kerdawy M M, *Eur J Med Chem*, 46 (2011) 3714.
46 Jain P P, Degani M S, Raju A, Anantram A, Seervi M, Sathaye S, Ray M & Rajan M, *Bioorg Med Chem Lett*, 26 (2016) 645.
47 Hale S L & Kloner R A, *J Cardiovasc Pharmacol Ther*, 11 (2006) 249.
48 Fragasso G, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala M, Calori G, Alfieri O & Margonato A, *J Am Coll Cardiol*, 48 (2006) 992.
49 Capdeville R, Buchdunger E, Zimmermann J & Matter A, *Nat Rev Drug Discov*, 1 (2002) 493.
50 Grant J A, Riethuisen J M, Moulaert B & DeVos C, *Ann Allergy Asthma Immunol*, 88 (2002) 190.

51 Trivedi M H, Fava M, Wisniewski S R, Thase M E, Quitkin F, Warden D, Ritz L, Nierenberg A A, Lebowitz B D & Biggs M M, *N Engl J Med*, 354 (2006) 1243.
52 Gilbert F & Dourish C, *Psychopharmacology*, 93 (1987) 349.
53 Cusack B, Nelson A & Richelson E, *Psychopharmacology*, 114 (1994) 559.
54 Rees L, *Br Med J*, 2 (1960) 522.
55 Tang L, Shukla P K & Wang Z J, *Neurosci Lett*, 397 (2006) 1.
56 Bhunia S, Kumar S V & Ma D, *J Org Chem*, 82 (2017) 12603.
57 Lazar C, Kluczyk A, Kiyota T & Konishi Y, *J Med Chem*, 47 (2004) 6973.
58 Viegas-Junior C, Danuello A, da Silva Bolzani V, Barreiro E J & Fraga C A M, *Curr Med Chem*, 14 (2007) 1829.
59 Kalaria P N, Satasia S P & Raval D K, *Eur J Med Chem*, 78 (2014) 207.
60 Vekariya R H, Patel K D, Rajani D P, Rajani S D & Patel H D, *Journal of the Association of Arab Universities for Basic and Applied Sciences*, 23 (2017) 10.
61 Anargyros P, Astill D & Lim I, *J Clin Microbiol*, 28 (1990) 1288.
62 Vekariya R H, Patel K D, Vekariya M K, Prajapati N P, Rajani D P, Rajani S D & Patel H D, *Res Chem Intermed*, 43 (2017) 6207.