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# A green synthesis of quinoline-4-carboxylic derivatives using *p*-toluenesulfonic acid as an efficient organocatalyst under microwave irradiation and their docking, molecular dynamics, ADME-Tox and biological evaluation

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**Abstract**

*P*-Toluenesulfonic acid, being an efficient, nonhazardous, and fast accessible organocatalyst, was used for the preparation of quinoline-4-carboxylic acid derivatives via a one-pot three-component reaction of aromatic benzaldehyde, substituted aniline, and pyruvic acid under microwave irradiation. After completion of the reaction, the pure products were isolated by column chromatography. Here, to achieve the desired synthesis, various catalytic and solvent conditions were applied to perform a comparison study. We are using higher yield, simple work-up process, avoiding the use of hazardous organic solvents, short reaction time and higher advantages of the present protocol in the study. Biological activities of synthesized compounds were tested against various antibacterial, antifungal, antimalarial, and antituberculosis strains. Compounds **4a** and **4c** (MIC 50 μg/mL) and compounds **4d** and **4n** (MIC 62.5 μg/mL) were found active against the *Escherichia coli* strain, compounds **4c** and **4p** (MIC 25 μg/mL) were found active against the *Staphylococcus aureus* strain, and compounds **4c** and **4d** were found active against the *Plasmodium falciparum* strain. Molecular docking revealed that ligands and proteins fitted exactly in the binding pocket and had significant correlation with the biological activity. We have also tested molecular dynamics and ADME-Tox parameters for the synthesized compounds.

## 1 | INTRODUCTION

Recently, the expansion of green protocols, which aid in the synthesis of products that are environmentally benign and pollution free, has received substantial levels of consideration because the chemical industry is increasingly moving toward greener unit processes. Method development is a very important step for the synthesis, and it may reduced time and cost of the synthesized products. At this time, multicomponent reactions (MCRs) have received more focus in the field of organic synthesis and medicinal chemistry because they offer high yield and other advantages over conventional synthesis methods.[1]Therefore, synthesis of designed reaction is very difficult in the green chemistry. Synthesis of biologically active molecules as well as other important intermediate molecules through an MCR approach delivers a number of merits over conventional methods, such as shorter reaction time, higher yield, lower cost, and the use of green protocol.[2–4] Quinoline nucleus has been found as an active antimalarial,[5–8] antituberculosis,[9–11] anticancer,[12] antibacterial,[13] anti-HIV,[14,15] antihypertensive,[16] anticonvulsant,[17,18]

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anti-infective,[19] antiplatelet,[20] antagonists,[21] and analgesic agents.[22] It is used in inhibition of serotonin (5-HT3) receptor antagonists,[23] tachykinin receptor 3 (NK-3),[24] and immunodeficiency virus.[24] Quinoline was introduced for the treatment of urinary tract infections in 1963.[25] Drugs based on quinoline nucleus include oxolinic acid and ciprofloxacin.[25] Owing to their highly potent biological activities, quinoline derivatives are much attractive in the synthesis chemistry. Development of efficient methods and green synthetic protocols is necessary for the investigation of the quinoline derivatives. In the literature, quinoline-4-carboxylic derivatives have been synthesized through multicomponent condensation of aromatic aldehyde, substituted aniline, and pyruvic acid using various catalysts, such as $H_2SO_4$,[26] hydroxylamine,[27] $C_{33}H_{46}NO_4PPdSi$,[28] ytterbium perfluorooctanoate,[29] $C_{26}H_{26}Cl_2P_2Pd$,[30] trifluoroacetic acid,[31] and $InCl_3$.[32] Many of these methods have some limitation and drawback, such as strong acid or basic condition, toxic reagent, expensive reagent and catalyst, longer reaction time, low yield, and extreme work-up process. Several protocols have also been developed for the quinoline-4-carboxylic acid derivatives through a one-pot green synthesis approach that is of great attention.

Green chemistry point of view, microwave irradiation reaction (MWI) in organic synthesis has encouraged scientists to explore for the organic synthesis. MWI has emerged a great energy source for the wide range of organic transformation with short reaction time and high yield of the products with high purity.[33–44] However, a study has been undertaken using MWI for the synthesis of the quinoline-4-carboxylic acid (Scheme 1).

## 2 | EXPERIMENTAL

### 2.1 | Apparatus and analysis

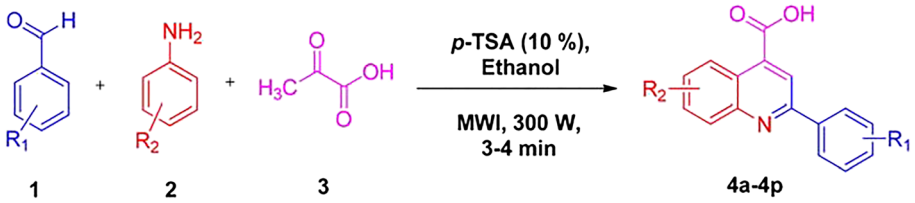
All chemicals were purchased from commercial sources and of analytical grade; the products were determined by a comparison of their physical parameter and melting points with those of known samples or by their spectral data. CEM Discover microwave (Model No. 908010; CEM Matthews, Inc.) was used for the synthesis system. Melting points of the compounds were measured by (Optimelt MPA 100) melting point apparatus. Fourier transform infrared spectroscopy (FT-IR) spectra were recorded on a Perkin Elmer (FTIR 377) spectrometer using KBr in $cm^{-1}$. Proton nuclear magnetic resonance spectra were recorded on a Bruker (AV 400 MHz) spectrometer using DMSO as solvent and TMS as the internal reference. $^{13}C$ was recorded on the Bruker (AV 100 MHz). Mass spectra were recorded at Advion expression CMS. Acetone is used as the mobile phase, and electron spray ionization (ESI) is used as the ion source. Elemental analysis was performed on a CHN elemental analyzer. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck precoated (silica gel 60 F254) aluminum sheets, visualized by UV light.

### 2.2 | General conventional method for synthesis of quinoline-4-carboxylic acid derivatives (4a-4p)

A solution of aromatic aldehyde (1) (1.0 mmol), substituted aniline (2) (1.2 mmol), and pyruvic acid (3) (1.0 mmol) in ethanol (25 mL) was taken in a flask. Stir and mix it well for 10 minutes, when the mixture was homogeneous, then add *p*-toluenesulfonic acid (*p*-TSA 10%) as a catalyst, after the addition of the catalyst reaction mixture was reflux at 80°C for the 3 hours and stand by the mixture overnight at room temperature. The reaction mixture was monitored by the TLC hexane: ethyl acetate (1:1). After the completion of the reaction mixture was poured into the ice-cold water, collect the crude products and all derivatives were purified by column chromatography.

### 2.3 | General microwave irradiation method for the synthesis of quinoline-4-carboxylic acid derivatives (4a-4p)

The route adopted for the synthesis of quinoline-4-carboxylic acids is given in Scheme 1. A mixture of aromatic aldehyde (**1**) (1.0 mmol), substituted aniline (**2**) (1.2 mmol), and pyruvic acid (**3**) (1.0 mmol) in 5 mL of ethanol. Stir and mix it well for 10 minutes, when the mixture was homogeneous, then add *p*-Toluenesulfonic




**SCHEME 1** Synthetic strategy for quinoline-4-carboxylic acid derivatives (**4a-4p**) [Color figure can be viewed at wileyonlinelibrary.com]

acid (*p*-TSA 10%) as a catalyst. The flask was put under microwave irradiation at 300 W for 3-4 minutes. Reaction progress was monitored using a TLC plate every 30 seconds using hexane:ethyl acetate (1:1) as the solvent system. After completion of the reaction, the reaction mixture was diluted with a minimum amount of ice-cold water, collect the crude products were purified by column chromatography. The yield of the product was around 50% to 80%. The reaction products were confirmed by comparing their physical data (ie, M.P., FT-IR, ESI-MS) with those reported in the literature. New compounds were confirmed by their spectral data (ie, FT-IR, ESI-MS, $^{1}$H NMR, $^{13}$C NMR).

## 2.4 | In vitro biological assay

### 2.4.1 | Antimicrobial assay

The antimicrobial activities were performed on various strains by the reported method,[45] and the results are described. This work has been carried out in Microcare Laboratory and TRC, Surat, India, as per reported method. Mueller-Hinton broth and Sabouraud broth were used as nutrient medium to grow bacteria and fungi, respectively. Inoculum size for the test strain was adjusted to 106 colony-forming units (CFU) per milliliter by comparing turbidity. Serial dilutions were prepared for primary and secondary screening. Control tube containing no antibiotics was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter plate of medium suitable for growth of the test organism and incubated at 37°C for bacteria or 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, and 2000 μg/mL concentration was achieved as 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 dilution set 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 was taken as the MIC. The synthesized quinoline hybrid thiosemicarbazides (**4a-4p**) 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 8) as well as three fungal strains (*Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 282). Ampicillin, ciprofloxacin, and chloramphenicol were used as standard control drugs for antibacterial activity, whereas nystatin and greseofulvin were used as standard drugs for antifungal activity.

## 2.5 | In vitro antimalarial assay

The antimalarial activity was performed on *Plasmodium falciparum* strain by reported method.[46] in vitro antimalarial activity was carried out by using with modification methods of microassay protocol. *P. falciparum* strain was supplemented with 1% D-glucose, 25 mM HEPES, 0.23% bicarbonate, and inactivated human serum. The culture was stored at 37°C for 24 hours. After the 5% D-sorbitol treatment, the asynchronous *P. falciparum* was synchronized. Primary-stage of parasitaemia of 0.9% to 1.4% at 4% hematocrit in total volume of 200 μL of 25 mM HEPES. The slides were observed of ring stage plasmodium into schizonts and trophozoites in the presence of various concentrations of ring stage agents. The results of mean inhibitory concentration ($IC_{50}$) record with the quinine and chloroquine have been used as the standard drugs.

## 2.6 | In vitro antituberculosis assay

The antituberculosis activity was performed on the *H37Rv* strain using an already known method, and results are described. The MIC of the test compounds against *Mycobacterium tuberculosis H37Rv* was determined by Lowenstein-Jensen (L-J) agar (MIC) method.[47] Primary 1000, 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, which was then sterilized by inspissation method. Culture of *M. tuberculosis H37Rv* growing on L-J medium was harvested in 0.85% saline in bijou bottles. For all test compounds, stock solution of 2000 μg/mL concentration was first prepared in DMSO. These tubes were then incubated at 37°C for 24 hours, followed by streaking of *M. tuberculosis H37Rv* (5 9104 bacilli per milliliter). These tubes were then incubated at $37 \pm 1$°C. Growth of bacilli was observed after 12, 22, and finally 28 days of incubation. Tubes containing compounds were compared with control tubes in which medium alone was incubated with *M. tuberculosis H37Rv*. The concentration at which no development of (or fewer than 20) colonies occurred was taken as the MIC of the test compound. The standard strain *M. tuberculosis H37Rv* was tested with a known drug rifampicin.

## 2.7 | Molecular docking method

Molecular docking study was performed on Schrodinger suite, Glide version 4.5.[48] This software was operated under the Linux operating system on Intel 2.8 MHz processor with 8 GB RAM. Grid-based method was used for ligand preparation with energy minimization on LigPrep-v2.1 (Maestro-v11.4, Schrodinger). In these studies, the X-ray crystallographic structure of the protein complex with ligand was taken from the protein data bank (www.rsc.org). The protein was prepared under protein preparation wizard (Maestro-v11.4, Schrodinger) for docking studies as follows: removal of ligand molecule from the protein active site, optimization of hydrogen bonding, and removal of cofactors and water molecules from the protein. All the ligands were docked into active site of protein by using default setting of the Glide, and Glide-score were collected in terms of multi-ligand scoring function.

## 2.8 | Automated docking setup

Docking studies were performed by using the maestro v11.4 software using the all default settings. Proteins PDB: 4DUH, *4CJN*, *1J3J* were downloaded from protein data bank, and this proteins were employed[49] as follows. Default setting and flexible space of quinoline-4-carboxylic acid derivatives were validated by docking parameters and biological activity, which docked exactly in the cavities present in the PDB with an affinity of lower energetic compounds. Subsequently, small-molecule compounds with respect to low energetic molecules were docked using same docking parameters. Docking studies were performed on a single machine equipped on Linux system using Glide with PDB protein being prepaid on protein preparation wizard. Glide searches for favorable interactions between the ligand molecules and protein receptor using a grid based method. PDB were downloaded from protein data bank, and a few steps were performed before going for docking: the protein preparation, removing the water molecule having less than three hydrogen bonds and cofactors from the protein, hydrogen bonding optimization, deleting the ligand present in PDB protein, and adjusting the bond order for ligand-protein. Then, the ligand was prepared using the LigPrep tool in Maestro version 10.4.

## 2.9 | Molecular dynamics

The explicit molecular dynamics (MD) study of the ligand-receptor compounds of the identified lead against the native ligand in the receptor was carried out using Desmond.[50] The best docked ligand was selected for the MD simulation. First, the **4c** ligand receptor complex aqueous solvation system was built by system builder with the aid of OPLS 2005 force field by predefined TIP3P solvation of orthorhombic solvation boundary with box volume (8924) A3 that is later followed by ions neutralization with addition of sodium. This system was later minimized with 2000 iterations with convergence criteria of 1 kcal/mol/Å. The minimized explicit solvation complex of ligand receptor complex is simulated for 10 ns using NPT ensemble at 300 K and 1.01325 bar with default set of relaxation before simulation.

## 2.10 | Selected spectral data of representative compounds

### 2.10.1 | 2-Phenylquinoline-4-carboxylic acid (4a)

Cream crystalline powder; M.P. 212-214°C; Yield: (89%); FT-IR (KBr): ($cm^{-1}$) 3290 (OH), 1700 (C═O), 1675, 1521, 1335, 1220, 1175, 1120, 755; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.95 (1H, s, COOH), 8.67-8.65 (1H, d, $J$ = 8), 8.47 (1H, s), 8.32-8.29 (2H, d, $J$ = 12), 8.19-8.17 (1H, t, $J$ = 8), 7.88-7.84 (2H, m), 7.73-7.69 (1H, t, $J$ = 16), 7.61-7.55 (3H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 165.5, 156.2, 151.3, 140.6, 137.6, 135.8, 133.2, 132.7, 130.7, 129.5, 128.9, 128.2, 125.7, 123.1; Anal. Calcd. for $C_{16}H_{11}NO_2$ (249.26): C 77.10, H 4.45, N 5.62; Found: C 77.80, H 4.49, N 5.32; ESI-MS: $m/z$ 251.52.

### 2.10.2 | 6-Nitro-2-phenyl quinoline-4-carboxylic acid (4b)

Yellowish solid; M.P.165-167°C; Yield: (67%); FT-IR (KBr): ($cm^{-1}$) 3241 (OH), 1770 (C═O), 1676, 1530, 1340, 1230, 1170, 1122, 759; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.94 (1H, s, COOH), 8.68 (1H, d, $J$ = 8.2), 8.45 (1H, s), 8.41 (1H, d, $J$ = 8.2), 8.21 (1H, t, $J$ = 7.5), 7.89-7.93 (2H, m), 7.43-7.50 (3H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 170.4, 155.6, 148.7, 140.4, 136.8, 136.6, 133.2, 132.7, 130.7, 129.6, 128.9, 121.7, 116.5; Anal. Calcd. for $C_{16}H_{10}N_2O_4$ (294.06): C 65.31, H 3.43, N 9.52; Found: C 65.31, H 3.49, N 9.32; ESI-MS: $m/z$ 295.45.

### 2.10.3 | 6-Methoxy-2-phenylquinoline-4-carboxylic acid (4c)

Cream crystalline powder; M.P. 211-213°C; Yield: (70%); FT-IR (KBr): ($cm^{-1}$) 3291 (OH), 1712 (C═O), 1645, 1522,

1338, 1230, 1180, 1130, 775; $^1$H NMR (400 MHz, DMSO-$d_6$); $\delta$ = 13.95 (1H, s, COOH), 8.66 (1H, d, $J$ = 8.2), 8.58 (1H, s), 8.52 (1H, d, $J$ = 8.2), 8.20 (1H, t, $J$ = 7.5), 7.90-7.93 (2H, m), 7.43-7.46 (3H, m), 3.8 (3H, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 163.1, 156.1, 152.1, 140.1, 136.2, 134.7, 133.2, 132.4, 130.1, 129.5, 128.8, 128.2, 125.7, 122.9; Anal. Calcd. for $C_{17}H_{13}NO_3$ (279.09): C 73.11, H 4.69, N 5.02; Found: C 73.14, H 4.65, N 5.03; ESI-MS: $m/z$ 280.

### 2.10.4 | 6-Chloro-2-phenylquinoline-4-carboxylic acid (4d)

Cream crystalline powder; M.P. 202-203°C; Yield: (75%); FT-IR (KBr): (cm$^{-1}$) 3256 (OH), 1716 (C═O), 1645, 1530, 1340, 1214, 1145, 1120, 758; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.91 (1H, s, COOH), 8.46 (1H, s), 8.25-8.24 (2H, d, $J$ = 4), 8.15-8.14 (1H, d, $J$ = 4), 8.09-8.07 (1H, d, $J$ = 8), 7.58-7.53 (2H, m), 7.52-7.48 (2H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 170.2, 157.5, 153.2, 140.7, 137.4, 135.8, 135.2, 132.7, 130.7, 129.5, 129.1, 128.3, 124.7, 120.1; Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (283.04): C 67.74, H 3.55, N 4.94; Found: C 67.75, H 3.61, N 5.51; ESI-MS: $m/z$ 284.02.

### 2.10.5 | 6-Methyl-2-phenylquinoline-4-carboxylic acid (4e)

White solid; M.P. 190-192°C; Yield: (70%); FT-IR (KBr): (cm$^{-1}$) 3445 (OH), 1710 (C═O), 1665, 1530, 1344, 1245, 1170, 1130, 890, 724; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.92 (1H, s, COOH), 8.44-8.42 (2H, d, $J$ = 8), 8.40 (1H, s), 8.29-8.27 (2H, d, $J$ = 12), 8.08-8.06 (1H, d, $J$ = 8), 7.71-7.68 (1H, m), 7.60-7.51 (3H, m), 3.47 (3H, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 168.3, 156.2, 156.3, 149.3, 140.3, 138.6, 130.5, 130.4, 129.5, 129.2, 127.7, 125.6, 122.1; Anal. Calcd. for $C_{17}H_{13}NO_2$ (263.04): C 77.55, H 4.98, N 5.32; Found: C 77.62, H 4.44, N 5.33; ESI-MS: $m/z$ 263.44.

### 2.10.6 | 6-Fluoro-2-phenylquinoline-4-carboxylic acid (4g)

Light yellow solid; M.P. 135-136°C; Yield: (57%); FT-IR (KBr): (cm$^{-1}$) 3030 (OH), 2611, 1696 (C═O), 1593, 1548, 1236, 930, 873, 689; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 14.13 (1H, s), 8.55 (1H, s), 8.48 (1H, d, $J$ = 2.9), 8.26 (3H, m), 7.78 (1H, t), 7.58 (3H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 170.2, 160.2, 151.2, 143.4, 137.1, 135.1, 133.9, 132.5, 131.7, 123.5, 129.8, 128.2, 125.4, 122.2; Anal. Calcd. for $C_{16}H_{10}FNO_2$ (267.10): C 71.91, H 3.77, N 5.24; Found: C 71.95, H 3.70, N 5.32; ESI-MS: $m/z$ 268.41.

### 2.10.7 | 2-(2-Chlorophenyl)quinoline-4-carboxylic acid (4h)

Cream crystalline powder; M.P. 233-235°C; Yield: (50%); FT-IR (KBr): (cm$^{-1}$) 3247 (OH), 1715 (C═O), 1645, 1530, 1343, 1232, 1165, 1130, 747; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.51 (1H, s, COOH), 8.70 (1H, d $J$ = 8.9), 8.58 (1H, s), 8.00-8.10 (2H, m), 7.40-7.70 (5H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 166.4, 156.1, 150.1, 141.7, 137.6, 135.7, 133.2, 133.0, 130.1, 129.5, 128.9, 126.4, 125.7, 122.9; Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (283.01): C 67.74, H 3.55, N 4.94; Found: C 67.75, H 3.56, N 5.01; ESI-MS: $m/z$ 284.10.

### 2.10.8 | 6-Chloro-2-phenylquinoline-4-carboxylic acid (4i)

White powder; M.P. 210-211°C; Yield: (72%); FT-IR (KBr): (cm$^{-1}$) 3280 (OH), 1692 (C═O), 1640, 1532, 1324, 1215, 1170, 1110, 748; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.79 (1H, s, COOH), 8.77-8.74 (1H, d, $J$ = 12), 8.18-8.15 (2H, d), 7.91-7.88 (1H, t, $J$ = 6), 7.87-7.73 (3H, m), 7.67-7.56 (2H, m), 3.45 (3H, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 166.8, 154.6, 152.7, 141.1, 134.1, 134.2, 132.9, 132.1, 130.8, 129.1, 128.7, 128.1, 125.7, 121.4; Anal. Calcd. for $C_{17}H_{12}ClNO_3$ (313.05): C 65.08, H 3.86, N 4.46; Found: C 65.64, H 3.85, N 4.50; ESI-MS: $m/z$ 313.32.

### 2.10.9 | 2-(4-Chlorophenyl)quinoline-4-carboxylic acid (4j)

Cream crystalline powder; M.P. 230-232°C; Yield: (70%); FT-IR (KBr): (cm$^{-1}$) 3289 (OH), 1695 (C═O), 1645, 1529, 1328, 1246, 1178, 1120, 745; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.47 (1H, s, COOH), 8.78-8.76 (1H, d, $J$ = 8), 8.25-8.23 (3H, d, $J$ = 8), 8.05-8.03 (1H, d, $J$ = 8), 7.74-7.71 (1H, t, $J$ = 6), 7.55-7.53 (3H, m), 7.70 (1H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 167.8, 155.6, 152.7, 141.1, 136.1, 135.2, 133.9, 132.1, 130.1, 129.1, 128.9, 128.2, 125.7, 122.6; Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (283.04): C 67.74, H 3.55, N 4.94; Found: C 67.71, H 3.56, N 5.01; ESI-MS: $m/z$ 282.25.

### 2.10.10 | 2-(4-Chlorophenyl)-6-nitroquinoline-4-carboxylic acid (4k)

Cream crystalline powder; M.P. 214-215°C; Yield: (68%); FT-IR (KBr): (cm$^{-1}$) 3292 (OH), 1765 (C═O), 1668, 1535, 1345, 1231, 1178, 1124, 748; $^1$H NMR (400 MHz, DMSO-

$d_6$): $\delta$ = 14.00 (1H, s, COOH), 8.66 (1H, d, $J$ = 8.2), 8.58 (1H, s), 8.52 (1H, d, $J$ = 8.2), 8.20 (1H, t, $J$ = 7.5), 7.90-7.93 (2H, m), 7.86 (1H, t, $J$ = 7.5), 7.43-7.46 (3H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 167.1, 155.6, 152.1, 141.7, 136.4, 135.8, 132.1, 132.4, 130.1, 129.5, 128.9, 128.2, 124.8, 121.2; Anal. Calcd. for $C_{16}H_9ClN_2O_4$ (228.03): C 58.46, H 2.76, N 8.52; Found: C 56.02, H 2.78, N 8.53; ESI-MS: $m/z$ 329.36.

### 2.10.11 | 2-(4-Chlorophenyl)-6-methoxyquinoline-4-carboxylic acid (4l)

Cream crystalline powder; M.P. 264-266°C; Yield: (65%); FT-IR (KBr): ($cm^{-1}$) 3323 (OH), 3064, 2968, 2837, 1689 (C═O), 1618 (C═N), 1587, 780; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.98 (1H, s, COOH), 8.70 (1H, d, $J$ = 8.2), 8.58 (1H, s), 8.22 (1H, t, $J$ = 7.5), 8.10-7.91 (2H, m), 7.47-7.41 (3H, m), 3.97 (3H, s, $OCH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 166.2, 157.2, 150.1, 141.4, 137.1, 134.4, 132.1, 132.7, 130.7, 130.1, 129.0, 128.7, 125.7, 122.8; Anal. Calcd. For $C_{17}H_{12}ClNO_3$ (313.5): C 65.08, H 3.86, N 4.46; Found: C 65.19, H 4.07, N, 4.15; ESI-MS: $m/z$ 314.25.

### 2.10.12 | 6-Chloro-2-(4-chlorophenyl) quinoline-4-carboxylic acid (4m)

Cream crystalline powder; M.P. 256-258°C; Yield: (50%); FT-IR (KBr): ($cm^{-1}$) 3250 (OH), 1642 (C═O), 1645, 1520, 1340, 1230, 1180, 1120, 886, 830 760; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.56 (1H, s, COOH), 7.58-7.70 (2H, m), 7.84-7.96 (1H, m), 8.14-8.23 (2H, m), 8.34-8.45 (2H, d), 8.84-8.96 (1H, d); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 167.2, 157.1, 152.7, 141.1, 140.9, 134.7, 132.6, 132.1, 130.7, 128.5, 127.8, 127.1, 125.4, 121.2; Anal. Calcd for $C_{16}H_9Cl_2NO_2$ (317.00): C 60.40, H 2.85, N 4.40; Found: C 59.00; H 2.96, N 4.54; ESI-MS: $m/z$ 318.32.

### 2.10.13 | 2-(4-Chlorophenyl)-6-methylquinoline-4-carboxylic acid (4n)

Cream crystalline powder; M.P. 212-213°C; Yield: (63%); FT-IR (KBr): ($cm^{-1}$) 3329 (OH), 3025, 1670 (C═O), 1689, 1523, 1365, 1245, 1178, 1122, 813, 759; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 10.52 (1H, s, COOH), 8.71 (1H, d, $J$ = 8.2), 8.61 (1H, s), 8.18 (1H, t, $J$ = 7.5), 7.91-7.95 (2H, m), 7.49-7.44 (3H, m), 2.3 (3H, d, CH3); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 164.2, 155.7, 154.8, 144.2, 138.3, 136.1, 134.2, 133.8, 132.7, 130.4, 128.9, 126.8, 125.7, 124.5; Anal. Calcd. for $C_{17}H_{12}ClNO_2$ (297.46): C 68.58, H 4.06, N 4.70; Found: C 68.65, H 4.20, N 4.72; ESI-MS: $m/z$ 297.44.

### 2.10.14 | 2-(4-Chlorophenyl)-6-hydroxyquinoline-4-carboxylic acid (4o)

Cream crystalline powder; M.P. 198-200°C; Yield: (69%); FT-IR (KBr): ($cm^{-1}$) 3230 (OH), 1745 (C═O), 1685, 1564, 1394, 1220, 1114, 1136, 775; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.98 (1H, s, COOH), 10.54 (1H, s, OH), 8.67 (1H, d, $J$ = 8.2), 8.58 (1H, s), 8.56 (1H, d, $J$ = 8.2), 8.30 (1H, t, $J$ = 7.5), 7.91-7.94 (2H, m), 7.88 (1H, t, $J$ = 7.5), 7.35-7.32 (3H, m); $^{13}$C NMR (100 MHz, DMSO-$_{d6}$): 168.0, 166.2, 160.1, 154.6, 144.6, 140.7, 139.5, 133.7, 131.8, 129.5, 129.1, 128.3, 125.7, 121.5; Anal. Calcd. for $C_{16}H_{10}ClNO_3$ (299.08): C 64.12, H 3.36, N 4.67; Found: C 64.17, H 3.35, N 4.71; ESI-MS: $m/z$ 299.13.

### 2.10.15 | 2-(4-Chlorophenyl)-6-fluoroquinoline-4-carboxylic acid (4p)

Cream crystalline powder; M.P. 200-20°C; Yield: (76%); FT-IR (KBr): ($cm^{-1}$) 3245 (OH), 1765 (C═O), 1642, 1535, 1348, 1242, 1196, 1152, 748; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 13.91 (1H, s, COOH), 8.29-8.28 (1H, d, $J$ = 4), 8.02-7.99 (1H, d, $J$ = 12), 7.69-7.68 (1H, m), 7.63-7.61 (1H, m), 7.52-7.45 (3H, m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 170.1, 156.4, 150.4, 141.6, 137.1, 135.1, 132.2, 132.7, 130.7, 129.5, 128.9, 128.2, 125.7, 122.7; Anal. Calcd. for $C_{16}H_9ClFNO_2$ (301.18): C 63.70, H 3.01, N, 4.64; Found: C 63.84, H 3.04, N 4.59; ESI-MS: $m/z$ 302.03.

## 3 | RESULTS AND DISCUSSION

A green, efficient route for the synthesis of the various quinoline-4-carboxylic acid derivative was achieved using conventional as well as microwave irradiation. However, the Pfitzinger reaction occurred when MWI was used for the synthesis of quinoline-4-carboxylic acids have been reported yet. Synthesis of quinoline-4-carboxylic acid in a nontoxic solvent like water, methanol, and ethanol has been reported. However, it did not give higher amounts of the products when trifluoroacetic acid was used in the reaction. Moreover, employing all types of conditions required heating in an oil bath for 3 to 5 hours. Comparative study of model reaction carried out in the conventional method.

The main aim of these work was to develop an efficient and green protocol for the synthesis of quinoline-4-carboxylic acids in the beginning. The reaction of

equimolar quantities of aromatic aldehyde (**1**) (1.0 mmol), substituted aniline (**2**) (1.2 mmol), and pyruvic acid (**3**) (1.0 mmol) was used as a model reaction to optimize the reaction conditions and to evaluate the catalytic activity of *p*-toluenesulfonic acid (*p*-TSA) compared with mention catalyst for the formation of quinoline-4-carboxylic acid derivatives comparative experiments were performed, and the data are shown in Table 2. Two catalysts were tested: TFA and *p*-TSA. However, *p*-TSA was found to be the most efficient in terms of reaction time and the yield of the product and as well as green chemistry protocols (Table 1). We have tested this reaction in different solvents, including methanol, ethanol, acetic acid, water, and some combination of the solvents in Table 3. But ethanol was found as a most benefited solvent.

However, we have found that MWI has successfully accelerated the condensation of aromatic aldehydes, substituted anilines and pyruvic such as in alcoholic condition, whereby the corresponding quinoline-4-carboxylic acids (**4a-4p**) were obtained in 3 to 4 minutes; the reactions were carried out in open vessel and the yield of products ranged between 50% and80%. The highest yields observed in the cases of benzaldehyde, aniline, and pyruvic acid, under the conventional conditions the reaction required heating under reflux for 3 hours give a lower yield as compared to MWI.

The model reaction was used to identify suitable conditions, including solvents and catalyst. The results are summarized in Tables 2 and 3. In this reaction, catalyst loadings in the range of 10% were tested. From the result table, we concluded that the lower yield of the product was observed in the absence of the catalyst (Table 2). In addition, it was discovered that the reaction was rather slow and resulted in average yield (50%) in the absence of the catalyst when the reaction was carried out in refluxing water for 3 minutes (Table 2), the product was found in good yield. Instead of all applied condition when we are applying ethanolic condition at 300 W MWI, product was found in excellent in terms of yield.

We have also proposed a possible mechanism for the final product (**4a-4p**) (Scheme 2). As we have described in the mechanism, Schiff bases (**g**) are formed in the first step by the reaction of aldehyde and aniline. Pyruvic acid formed a scaffold (**e**) when *p*-TSA was added into the reaction mixture and nucleophiles attacked on the Schiff base carbon. After some intermediate steps (**h**, **i**, **j)** the final step occurs by the oxidation of intermediate (**k**) and forms carboxylic-4-acids (**4a-4p**).

## 3.1 | Biological activity

### 3.1.1 | Antibacterial and antifungal activity

The in vitro antibacterial study of synthesized quinoline-4-carboxylic acid (**4a-4p**) was determined by the agar

**TABLE 1** Quinoline-4-carboxylic acid derivatives catalyzed by *p*-TSA using MWI

| Entry | Compound code | $R_1$ | $R_2$ | Time (min) | Yield[a] (%) | M.P. (°C) | References |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | H | H | 3 | 80 | 212-214 | [50] |
| 2 | **4b** | H | 4-$NO_2$ | 3 | 67 | 165-167 | [52] |
| 3 | **4c** | H | 4-$OCH_3$ | 3 | 70 | 211-213 | [51] |
| 4 | **4d** | H | 4-Cl | 3 | 75 | 202-203 | - |
| 5 | **4e** | H | 4-$CH_3$ | 3 | 70 | 190-192 | [53] |
| 6 | **4f** | H | 4-OH | 3 | 65 | 200-202 | - |
| 7 | **4g** | H | 4-F | 3 | 57 | 135-136 | - |
| 8 | **4h** | 2-Cl | H | 4 | 50 | 233-235 | [54] |
| 9 | **4i** | 2-Cl | 4-$OCH_3$ | 3 | 65 | 208-210 | - |
| 10 | **4j** | 4-Cl | H | 4 | 70 | 230-232 | [55] |
| 11 | **4k** | 4-Cl | 4-$NO_2$ | 3 | 68 | 214-215 | - |
| 12 | **4l** | 4-Cl | 4-$OCH_3$ | 3 | 65 | 264-266 | [56] |
| 13 | **4m** | 4-Cl | 4-Cl | 3 | 50 | 256-258 | [57] |
| 14 | **4n** | 4-Cl | 4-$CH_3$ | 3 | 63 | 212-213 | [50] |
| 15 | **4o** | 4-Cl | 4-OH | 3 | 69 | 198-200 | - |
| 16 | **4p** | 4-Cl | 4-F | 3 | 76 | 200-202 | - |

Abbreviation: M.P., melting point.

[a]Purified product.

| Entry | Catalyst | Catalyst loading (mol%) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | TFA | 10 | 3 | 75 |
| 2 | *P*-TSA | 10 | 3 | 80 |
| 3 | - | - | 3 | 50 |

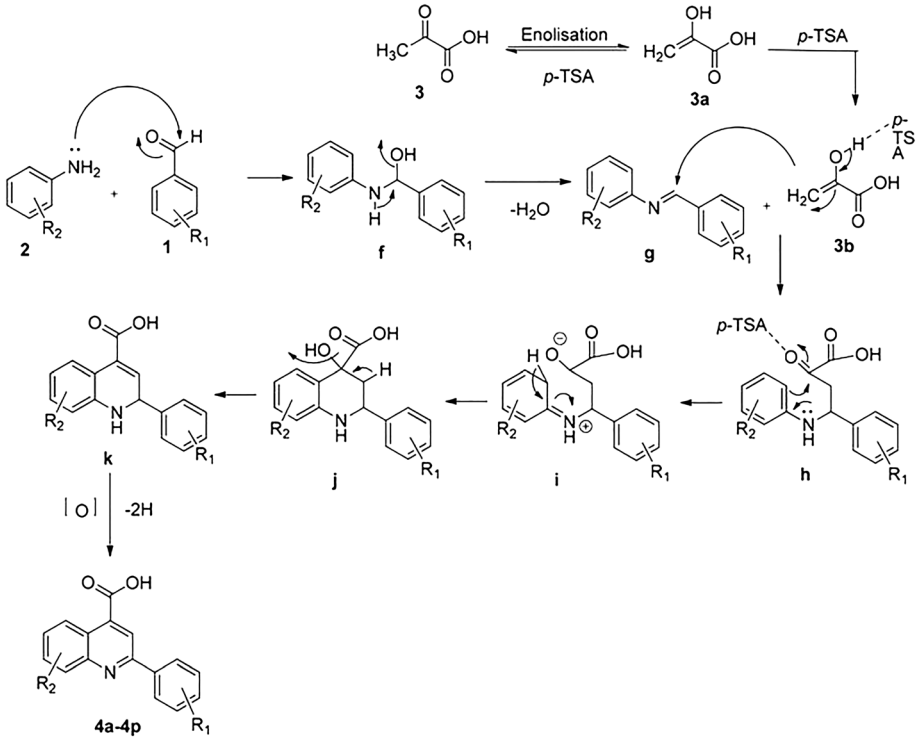
[a]Purified product.

**TABLE 2** Evaluation of catalytic activity of different catalysts for the condensation of benzaldehyde, aniline, and pyruvic acid in ethanol at 300 W microwave irradiation

| Entry | Solvent | Catalyst loading (mol%) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | Methanol | *P*-TSA (10%) | 3 | 30 |
| 2 | Ethanol | *P*-TSA (10%) | 3 | 80 |
| 3 | AcOH | *P*-TSA (10%) | 3 | Trace |
| 4 | Methanol:$H_2O$ (50%) | *P*-TSA (10%) | 3 | 20 |
| 5 | Ethanol:$H_2O$ (50%) | *P*-TSA (10%) | 3 | 20 |
| 6 | Methanol | TFA (10%) | 3 | 50 |
| 7 | Ethanol | TFA (10%) | 3 | 75 |
| 8 | AcOH | TFA (10%) | 3 | Trace |
| 9 | Methanol:$H_2O$ (50%) | TFA (10%) | 3 | 30 |
| 10 | Ethanol:$H_2O$ (50%) | TFA (10%) | 3 | 45 |
| 11 | Ethanol | - | 3 | 50 |

[a]Purified product.

**TABLE 3** Evaluation of different solvent activity in (10 mmol%) catalysts for the condensation of benzaldehyde, aniline, and pyruvic acid in ethanol at 300 W microwave irradiation




**SCHEME 2** Proposed mechanism for derivative of quinoline-4-carboxylic acid (**4a-4p**)

dilution method. As shown in Table 4, all synthesized compounds were tested in various antibacterial and antifungal strains such as *E. coli* MTCC 443 and *P. aeruginosa* MTCC 441 Gram-negative strains, *S. aureus* MTCC 96 and *S. pyogenes* MTCC 442 Gram-positive strains, *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 strains, respectively. Their biological activities compared with standard drugs such as ampicillin, chloramphenicol, ciprofloxacin, nystatin, and greseofulvin.

**TABLE 4** Biological activity of synthesized compounds **4a-4p**

| | | Antibacterial | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Gram-negative organism[d] | | Gram-positive organism[e] | | Antifungal[a] | | | Antimalarial[b] | AntiTB[c] | |
| Entry | Code | Ec | Pa | Sa | Sp | Ca | An | Ac | Pf | H37Rv | MDR TB[f] |
| 1 | **4a** | 50 | 250 | 125 | 100 | 500 | 500 | 1000 | 0.26 | 250 | 1000 |
| 2 | **4b** | 125 | 100 | 125 | 125 | 500 | 250 | 250 | 0.54 | 500 | >1000 |
| 3 | **4c** | 50 | 250 | 25 | 250 | 1000 | 250 | 250 | 0.12 | 125 | 250 |
| 4 | **4d** | 62.5 | 100 | 500 | 500 | 1000 | >1000 | >1000 | 0.14 | 500 | 1000 |
| 5 | **4e** | 125 | 100 | 250 | 250 | >1000 | >1000 | >1000 | 0.94 | 1000 | >1000 |
| 6 | **4f** | 500 | 500 | 100 | 100 | 500 | 1000 | 1000 | 1.02 | 1000 | >1000 |
| 7 | **4g** | 250 | 100 | 250 | 250 | 500 | 1000 | 1000 | 1.07 | 250 | 500 |
| 8 | **4h** | 100 | 125 | 250 | 250 | 250 | 500 | 500 | 1.67 | 125 | 250 |
| 9 | **4i** | 125 | 100 | 250 | 62.5 | 1000 | 500 | 1000 | 1.03 | 100 | 125 |
| 10 | **4j** | 250 | 250 | 125 | 100 | 1000 | 500 | 1000 | 0.73 | 500 | 1000 |
| 11 | **4k** | 250 | 250 | 500 | 500 | >1000 | >1000 | >1000 | 0.57 | 250 | 500 |
| 12 | **4L** | 50 | 100 | 500 | 500 | 500 | 1000 | 1000 | 0.59 | 500 | >1000 |
| 13 | **4m** | 250 | 250 | 250 | 250 | 500 | 1000 | 1000 | 1.65 | 500 | 1000 |
| 14 | **4n** | 62.5 | 100 | 250 | 250 | 250 | 500 | 500 | 0.69 | 125 | 200 |
| 15 | **4o** | 125 | 100 | 500 | 500 | 1000 | 500 | 1000 | 0.75 | 100 | 125 |
| 16 | **4p** | 100 | 125 | 25 | 50 | 1000 | 500 | 500 | 1.06 | 250 | 500 |
| 17 | Amp[f] | 100 | - | 250 | 100 | - | - | - | - | - | - |
| 18 | Cam[f] | 50 | 50 | 50 | 50 | - | - | - | - | - | - |
| 19 | Cipro[f] | 25 | 25 | 50 | 50 | - | - | - | - | - | - |
| 20 | Ny[f] | - | - | - | - | 100 | 100 | 100 | - | - | - |
| 21 | Gris[f] | - | - | - | - | 500 | 100 | 100 | - | - | - |
| 22 | INH[f] | - | - | - | - | - | - | - | - | 0.20 | 100 |
| 23 | RMP[f] | - | - | - | - | - | - | - | - | 1.00 | 50 |
| 24 | Quin[f] | - | - | - | - | - | - | - | 0.26 | - | - |
| 25 | CQ[f] | - | - | - | - | - | - | - | 0.02 | - | |
| 26 | KAN[f] | - | - | - | - | - | - | - | - | - | 50 |

[a]Values represented in μg/mL, *Candida albicans* (Ca), *Aspergillus niger* (An), *Aspergillus clavatus* (Ac).
[b]Values represented in IC50 μg/mL, antimalarial screening using *Plasmodium falciparum* strain.
[c]Values represented in μg/mL, antituberculosis screening via H37Rv strain.
[d]Values represented in μg/mL, *Escherichia coli* (Ec), *Pseudomonas aeruginosa* (Pa).
[e]Values represented in μg/mL, *Staphylococcus aureus* (Sa), streptococcus pyrogenes (Sp).
[f]Reference drug, ampicillin, chloramphenicol, ciprofloxacin, nystatin, griseofulvin, isoniazid, rifampicin, quinine, chloroquine.

We have noted that all molecules exhibited excellent activity against *E. coli* Gram-negative strain, significant active against *S. aureus* strain and moderate active against *P. aeruginosa* and *S. pyrogenes* strains. As per Table 4 conclusion, four synthesized compounds, **4a** (MIC 50 μg/mL), **4c** (MIC 50 μg/mL), **4d** (62.5 μg/mL), and **4n** (MIC 62.5 μg/mL), were found be most active against the Gram-negative strain *E. coli* as compared to standard drugs ampicillin (MIC 100 μg/mL), **4a** and **4c** found to be similarly active against chloramphenicol (MIC 50 μg/mL) in the *E. coli* strain. Two compounds **4c** (MIC 25 μg/mL) and **4p** (MIC 25 μg/mL) were shown most potent against the *S. aureus* strains as compared to chloramphenicol (MIC 50 μg/mL) and ciprofloxacin (MIC 50 μg/mL), Four compounds **4a** (MIC 125 μg/mL), **4b** (MIC 125 μg/mL), **4f** (MIC 100 μg/mL), and **4j** (MIC 125 μg/mL) showed good activity against the Gram-positive strain *S. aureus* as compared to ampicillin (MIC 250 μg/mL). Compound **4i** (MIC 62.5 μg/mL) was found to be active against the *S. pyrogenes* strain as compared to

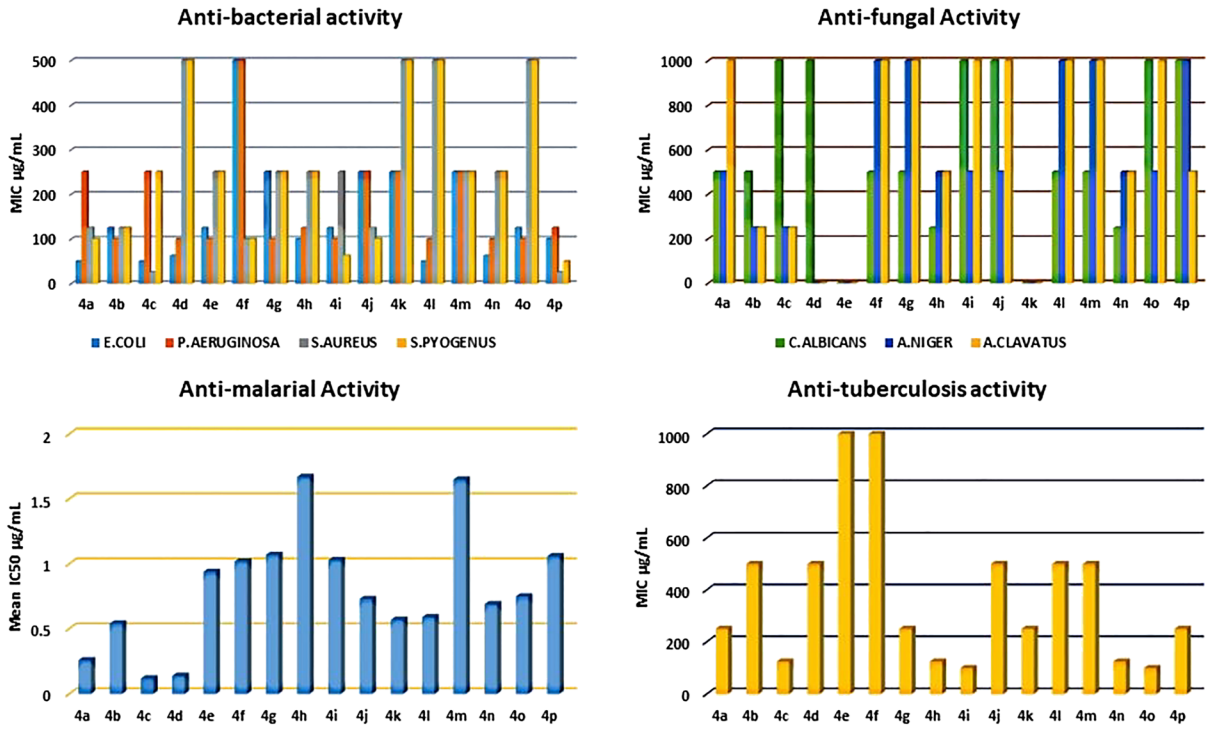



**FIGURE 1** Graphical representation of biological activity [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 5** Molecular docking score of synthesized compound **4a-4p**

| | | PDB: 4DUH | | PDB: *4CJN* | | PDB: *1J3J* | |
|---|---|---|---|---|---|---|---|
| **Entry** | **Code** | **XP GScore** | **XP HBond** | **XP GScore** | **XP HBond** | **XP GScore** | **XP HBond** |
| 1 | **4a** | −5.463 | 0 | −2.495 | −0.287 | −7.064 | −1.94 |
| 2 | **4b** | −6.022 | −0.566 | −4.07 | −1.8 | −6.054 | −1.065 |
| 3 | **4c** | −4.62 | −0.05 | −2.41 | −0.223 | −6.157 | −1.22 |
| 4 | **4d** | −6.17 | −0.568 | −4.241 | −1.723 | −7.059 | −1.433 |
| 5 | **4e** | −6.179 | −0.567 | −4.238 | −1.693 | −7.329 | −1.356 |
| 6 | **4f** | −6.511 | −0.822 | −4.418 | −1.226 | −7.216 | −1.864 |
| 7 | **4g** | −5.349 | 0 | −2.477 | −0.285 | −6.934 | −1.229 |
| 8 | **4h** | −6.104 | −0.568 | −4.56 | −1.752 | −6.407 | −0.338 |
| 9 | **4i** | −6.691 | −0.735 | −2.567 | −0.232 | −5.666 | −1.194 |
| 10 | **4j** | −5.475 | 0 | −2.242 | 0 | −7.239 | −1.9 |
| 11 | **4k** | −5.952 | −0.472 | −4.182 | −1.675 | −6.042 | −1.435 |
| 12 | **4l** | −5.354 | −0.35 | −3.178 | −0.7 | −6.158 | −1.243 |
| 13 | **4m** | −6.294 | −0.564 | −4.402 | −1.781 | −7.174 | −1.088 |
| 14 | **4n** | −6.267 | −0.566 | −2.758 | 0 | −6.75 | −1.175 |
| 15 | **4o** | −5.141 | −1.07 | −4.348 | −1.239 | −7.333 | −1.244 |
| 16 | **4p** | −6.249 | −0.564 | −4.535 | −1.747 | −7.273 | −1.701 |
| 17 | Amp[a] | −3.65 | −0.957 | −4.051 | −2.033 | - | - |
| 18 | Cam[a] | −6.721 | −2.085 | −3.973 | −1.92 | - | - |
| 19 | Cipro[a] | −6.472 | −0.48 | −3.024 | −0.885 | - | - |
| 20 | Quin[a] | - | - | - | - | −4.878 | −0.336 |
| 21 | CQ[a] | - | - | - | - | −4.915 | 0 |

[a]Standard drugs.

ampicillin. Compound **4p** (MIC 50 μg/mL) shows a similar activity against *S. pyrogenes* compared with chloramphenicol and ciprofloxacin, while other remaining compounds were moderately active against antibacterial strains. Compounds **4h** (MIC 250 μg/mL) and **4n** (MIC 250 μg/mL) showed higher activity against the antifungal strain *C. albicans* as compared to greseofulvin (MIC 500 μg/mL), but not active against the nystatin (MIC 100 μg/mL) as a standard drug. Compounds **4a**, **4b**, **4f**, **4 g**, **4l**, and **4 m** (MIC 500 μg/mL) showed a similar activity against *C. albicans* when compared to greseofulvin (Table 4 and Figure 1). Many of the compounds were not active against antifungal strains such as *A. niger* and *A. clavatus* when compared to standard drugs.

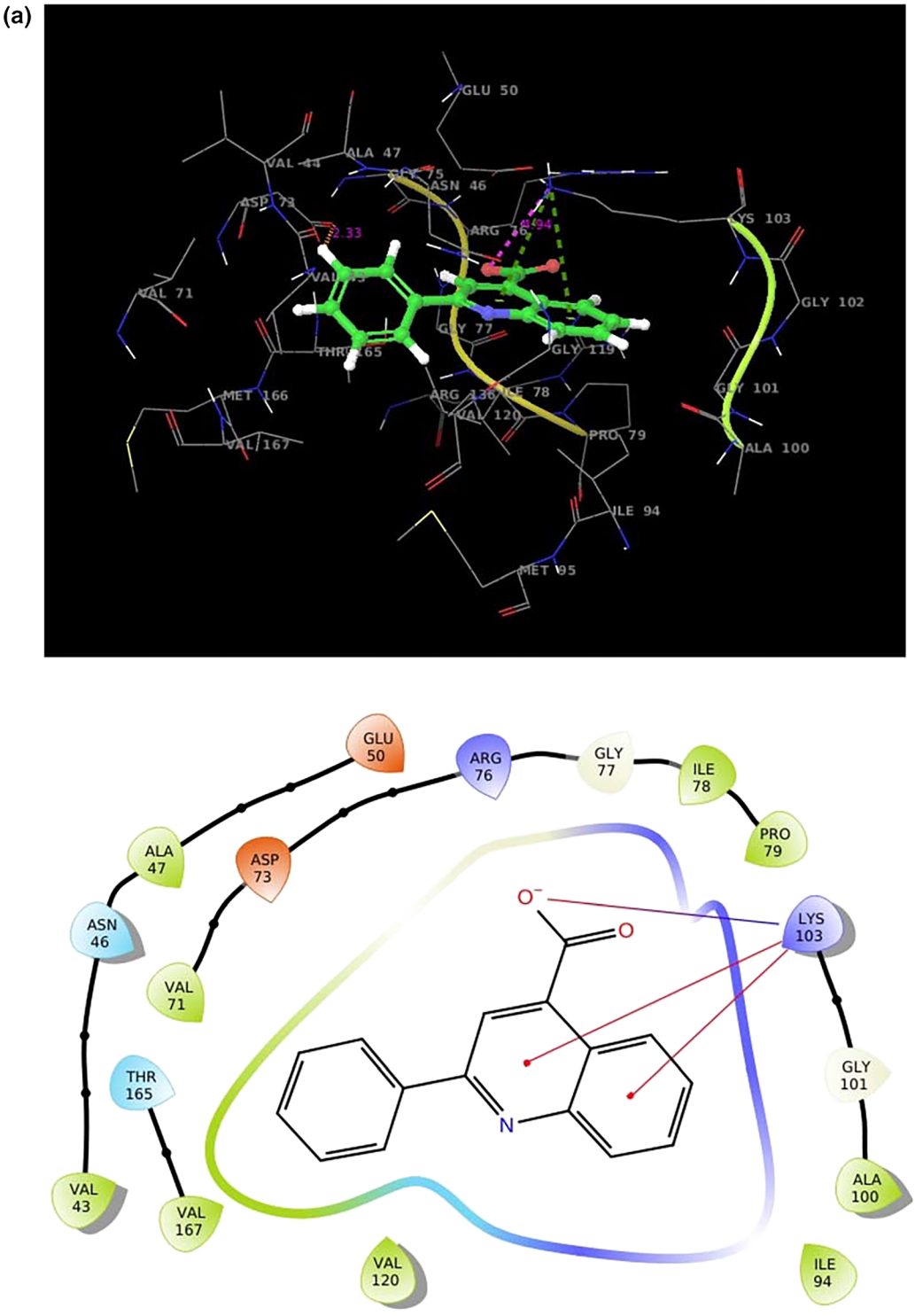



**FIGURE 2** 3D and 2D interaction of PDB: *4UDH*: A, pose with compound **4a and** B, pose with compound **4c** [Color figure can be viewed at wileyonlinelibrary.com]

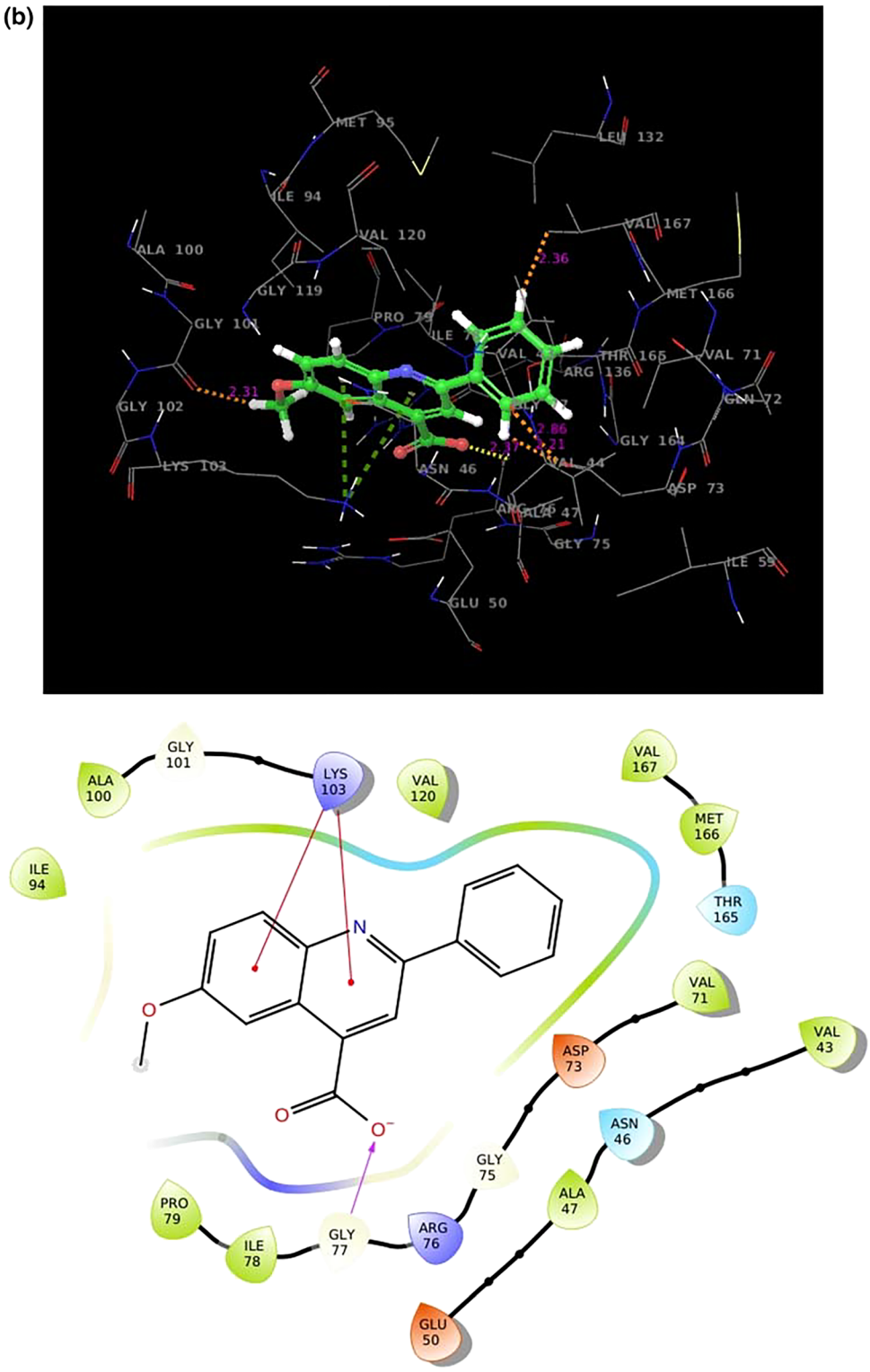



**FIGURE 2** (Continued)

## 3.2 | Antimalarial and antituberculosis activity

All synthesized compounds (**4a-4p**) were evaluated for their antimalarial activity and antituberculosis activity against *P. falciparum* and H37Rv strain, respectively. Moreover, all synthesized compounds were tested for their multidrug resistance tuberculosis study. As per Table 4, we have stated that compounds **4c** (IC50 0.12 μg/mL) and **4d** (IC50 0.14 μg/mL) were found to be the most potent candidate among the all synthesized compounds against the *P. falciparum*

strain as compared to the standard drug quinine (IC50 0.26 μg/mL). Compound **4a** (IC50 0.26 μg/mL) showed a similar activity against the *P. falciparum* strain when compared to quinine. Compounds **4b** (IC50 0.54 μg/mL), **4k** (IC50 0.57 μg/mL), and **4l** (IC50 0.59 μg/mL) were shown moderate active against quinine, while all compounds were shown moderate activity against chloroquine. The in vitro tuberculosis activity of the synthesized compounds (**4a-4p**) was performed against *M. tuberculosis* H37Rv strain and MDR-TB. As per Table 4, none of the synthesized compounds was active against both TB strains as compared to the standard drugs isoniazid and rifampicin.

## 3.3 | Structure-activity relationship

In the quest for finding the hit molecule of biological activity, we have investigated the existing series of

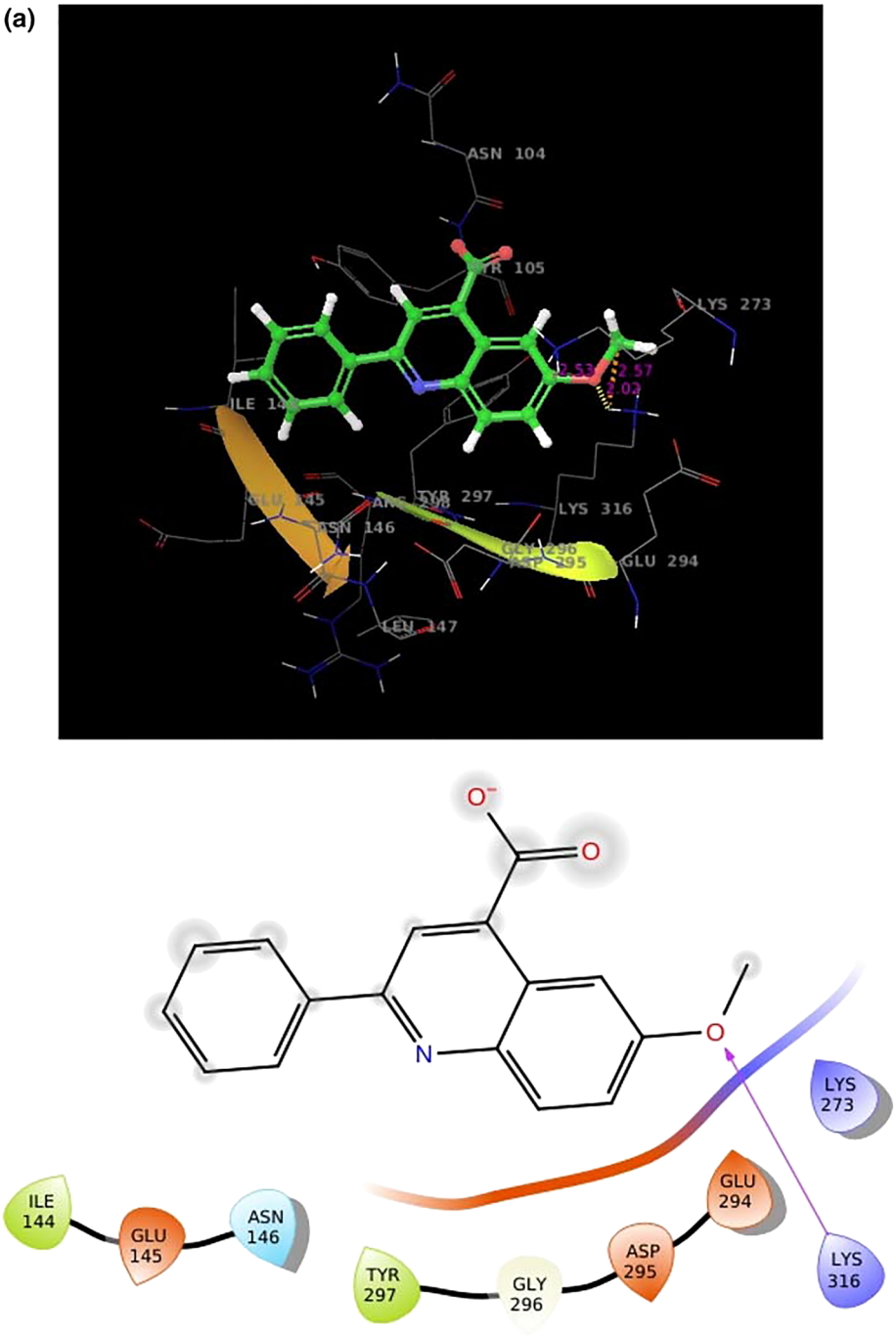



**FIGURE 3** 3D and 2D interaction of PDB: *4CJN*: A, pose with compound **4c** and B, pose with compound **4p** [Color figure can be viewed at wileyonlinelibrary.com]

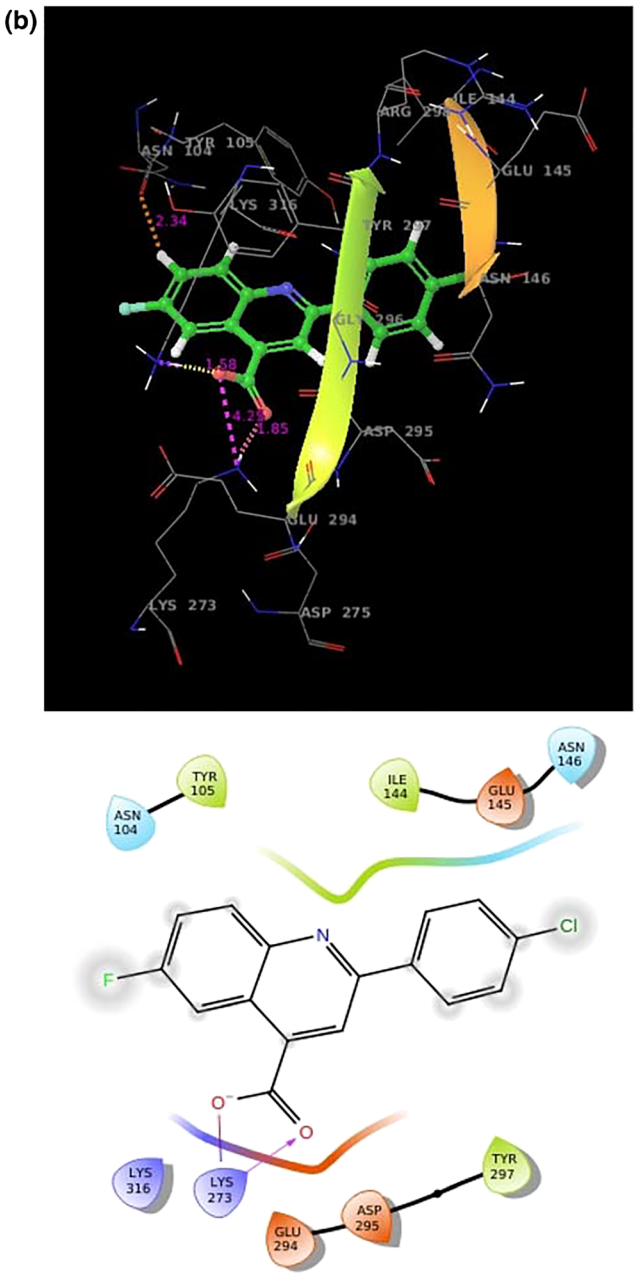



**FIGURE 3** (Continued)

quinoline hybrid thiosemicarbazide derivatives. For this study, we have tested synthesized compounds against various biological activities. Based on these studies, we noted that electronic configuration of functional group effecting on biological activity. Compounds comprising methoxy electron donating group (EDG) on quinoline ring led to potent biological activity. Compounds having substation at the sixth position of quinoline with EDG such as methoxy (**4c**, **4i**), methyl (**4n**), and hydroxy (**4f**), and having substituted on quinoline ring with EWG such as chlorine (**4d**), fluorine (**4p**), and nitro (**4b**) increased bioactivity in Gram-negative (*E. coli*) and Gram-positive (*S. aureus*, *S. pyrogenes*) bacteria. Moreover, phenyl ring substitution with chlorine group also effected antibacterial activity. EDG or EWG at the sixth substituted position on quinoline having excellent bioactivity against antifungal activity is compared to standard drug such as nitro (**4b**), hydroxy (**4f**, **4l**), fluorine (**4g**), chlorine (**4m**), and methyl (**4n**). Compounds having a fused combination of EDG and EWG in derivative also increased potency of molecules in antifungal activity. In *P. falciparum*, we observed no substitution at any position having similar potency. While, compounds

having quinoline substitution at six position with strong EDG like methoxy (compound **4c**) and weak EWG like chlorine (compound **4d**) having highest potency against *P. falciparum* when compared with quinine. But quinoline substitution with strong EWG like nitro (compound **4b**) and substituted on phenyl ring at any position like ortho or para (compounds **4k**, **4l**) decreased potency against the *P. falciparum*.

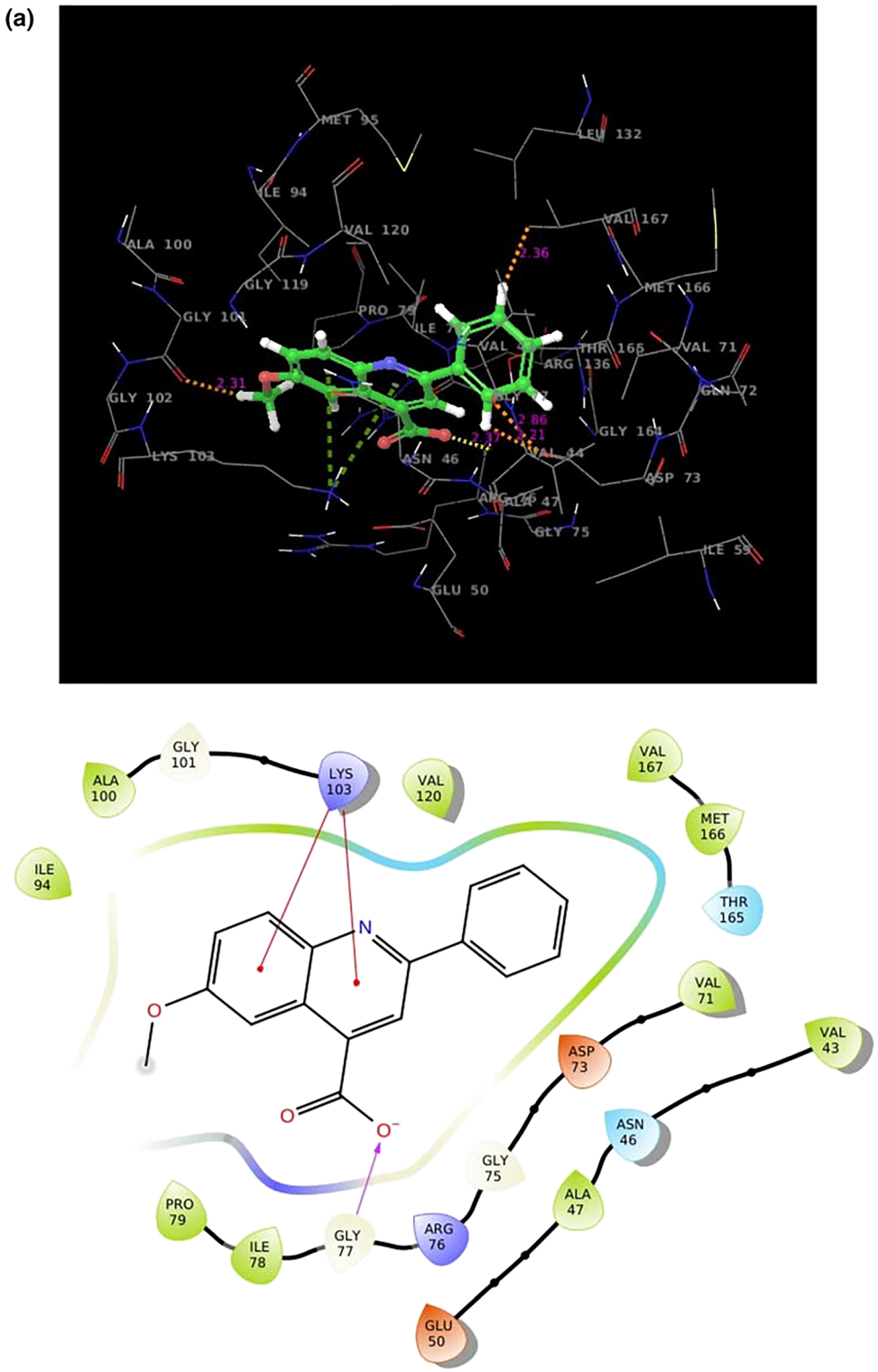



**FIGURE 4** 3D and 2D interaction of PDB: *1J3J*: A, pose with compound **4c** and B, pose with compound **4d** [Color figure can be viewed at wileyonlinelibrary.com]

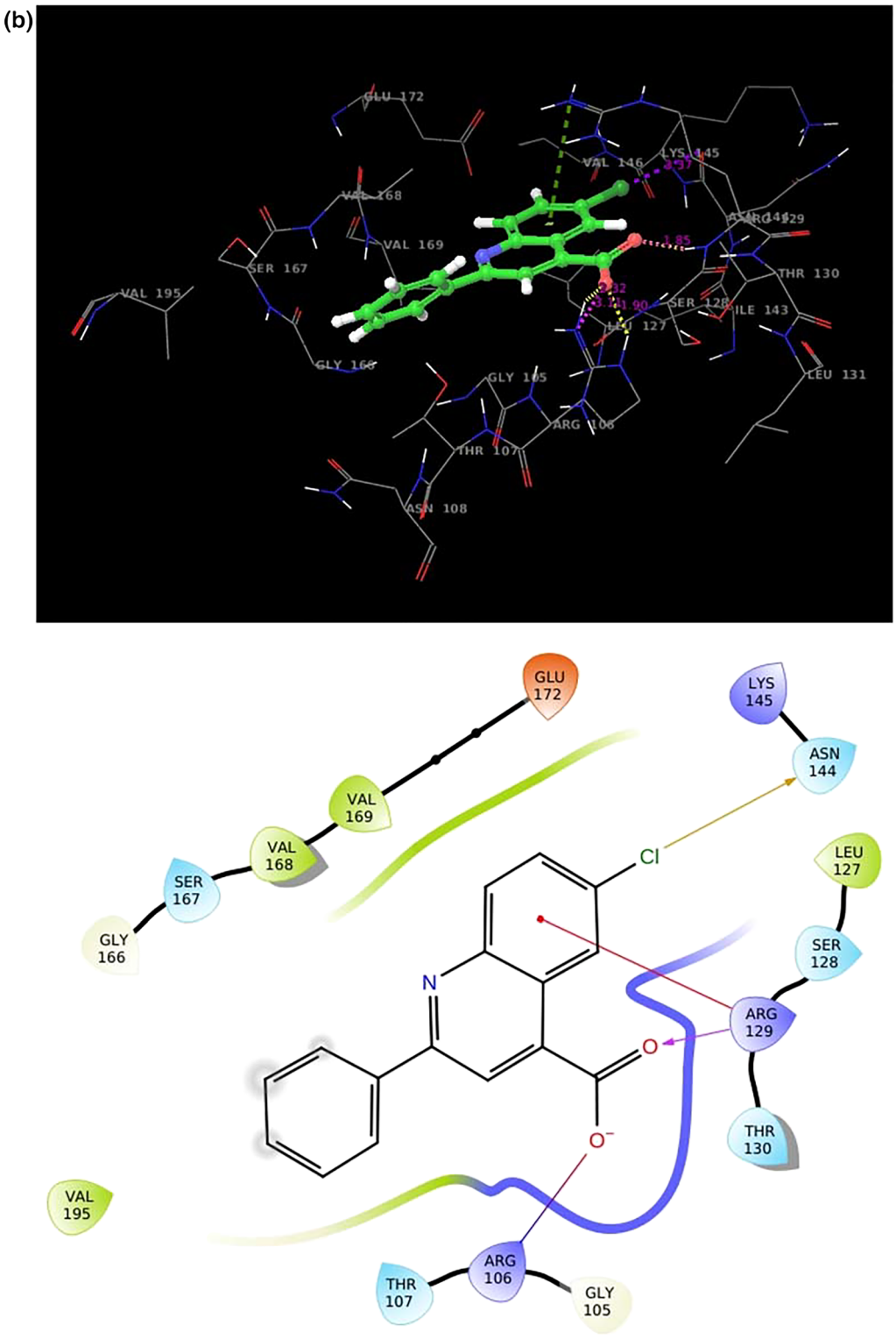



**FIGURE 4** (Continued)

## 3.4 | Docking study

Docking study was performed to find out the plausible binding mechanism of all synthesized compounds; these studies were performed on selected *4UDH* (*E. coli*), *4CJN* (*S. aureus*), and *1J3J* (*P. falciparum*) target. Protein 3D structures were downloaded from the protein data bank (PDB), and docking study was performed using Glide tools on Maestro 11.0 (Schrodinger, LLC, New York, NY, 2015) program. The summarized results are concluded in Table 5, and we have selected the best binding 2D and 3D poses of compounds **4a** and **4c** with PDB: *4UDH* are

**TABLE 6** Molecular docking interaction with amino acid

| | | | H-bond | | | Halogen bond | |
|---|---|---|---|---|---|---|---|
| **Code** | **Protein** | **Atom[a]** | **Amino acid[b]** | **BL[c]** | **π-π interaction** | **Amino acid[b]** | **BL[c]** |
| **4a** | 4UDH (*E. coli*) | C of Phenyl ring | ASP 73 | 2.33 | Quinoline | - | - |
| | | O of —CO | LYS 103 | 4.94 | | | |
| **4c** | | C- of phenyl ring | VAL 167 | 2.36 | Quinoline-LYS 103 | - | - |
| | | | ASP 73 | 2.21 | | | |
| | | | ASP 73 | 2.86 | | | |
| | | C of —CO | ARG 76 | 2.37 | | | |
| **4l** | | C of phenyl ring | GLY 101 | 2.11 | Quinoline-LYS 103 | - | - |
| | | | VAL 120 | 2.68 | | | |
| | | O of —$OCH_3$ | ARG 136 | 2.70 | | | |
| | | C atom of phenyl-quinoline | ARG 136 | 2.58 | | | |
| | | H of —$CH_3$ | ARG 136 | | | | |
| | | O of —$OCH_3$ | ARG 136 | 1.75 | | | |
| **4c** | 4CJN (*S. aureus*) | C of phenyl-quinoline | LYS 273 | 2.53 | - | - | - |
| | | O of —$OCH_3$ | LYS 316 | 2.02 | | | |
| | | H of —$OCH_3$ | LYS 316 | 2.57 | | | |
| **4p** | | C of phenyl-quinoline | ASN 104 | 2.34 | - | - | - |
| | | O of —CO | LYS 273 | 1.85 | | | |
| | | | LYS 316 | 1.58 | | | |
| | | C of —CO | LYS 273 | 4.25 | | | |
| **4a** | 1J3J (*P. falciparum*) | O of —CO | ARG 106 | 2.69 | - | - | - |
| | | | ARG 106 | 1.76 | | | |
| | | | ARG 106 | 2.13 | | | |
| | | O of —CO | ARG 129 | 2.69 | | | |
| | | | ARG 129 | 2.07 | | | |
| | | | ARG 128 | 2.37 | | | |
| **4c** | | C of —$CH_3$ | ASN 144 | 2.55 | Quinoline-ARG 129 | - | - |
| | | C of —CO | ARG 129 | 1.85 | | | |
| | | O of —CO | SER 128 | 2.69 | | | |
| | | | ARG 106 | 1.85 | | | |
| **4d** | | C of —CO | ARG 129 | 1.85 | Quinoline-ARG 129 | —Cl with ASN 144 | 3.37 |
| | | | ARG 106 | 3.11 | | | |
| | | O of —CO | ARG 106 | 1.90 | | | |
| | | | ARG 106 | 2.32 | | | |

[a]Ligand atom.
[b]Protein amino acid.
[c]Bond-length between interaction.

shown in Figure 2, compounds **4c** and **4p** with PDB: *4CJN* are shown in Figure 3, compounds **4c** and **4d** with *1J3J* are shown in Figure 4. Each of the ligands has indicated good docking score between −6.691 and −4.62 in *4UDH*, −4.56 and −4.41 in 4CNJ, and −7.329 and −6.042 in *1J3J* protein. LYS 103 and ARG 129 were found as common π-π interaction in the compounds **4a**, **4c**, and **4l** in *4UDH* and **4c** and **4d** in *1J3J*, respectively. Plausible binding mechanisms of selected compounds are described in Table 5. From Table 6, it is clear that compound **4a** (XP GScore −5.463) generates two strong H-bonds between phenyl-ASP 73 (2.33 Å) and —CO-LYS 103 (4.94 Å); compound **4c** (XP GScore −4.62) generates five H-bonds between phenyl-VAL 167 (2.36 Å); and

**TABLE 7** ADME-Tox parameters

| Code | PHOA[a] | QPPCaco[b] | QPlogBB[c] | QPlogKhsa[d] | QPlogHERG[e] | QPlogS[f] | PSA[g] |
|---|---|---|---|---|---|---|---|
| **4a** | 3 | 262.911 | −0.48 | 0.024 | −3.77 | −3.808 | 57.623 |
| **4b** | 2 | 31.083 | −1.484 | −0.011 | −3.754 | −4.027 | 102.536 |
| **4c** | 3 | 273.104 | −0.547 | 0.043 | −3.684 | −4.033 | 65.809 |
| **4d** | 3 | 263.167 | −0.328 | 0.139 | −3.721 | −4.544 | 57.603 |
| **4e** | 3 | 263.073 | −0.51 | 0.181 | −3.727 | −4.377 | 57.604 |
| **4f** | 3 | 80.014 | −1.046 | −0.145 | −3.663 | −3.53 | 80.151 |
| **4g** | 3 | 263.201 | −0.375 | 0.066 | −3.661 | −4.169 | 57.61 |
| **4h** | 3 | 253.455 | −0.37 | 0.139 | −3.711 | −4.443 | 58.508 |
| **4i** | 3 | 268.848 | −0.427 | 0.156 | −3.615 | −4.656 | 66.655 |
| **4j** | 3 | 263.168 | −0.328 | 0.139 | −3.72 | −4.544 | 57.607 |
| **4k** | 2 | 31.218 | −1.35 | 0.102 | −3.683 | −4.726 | 102.553 |
| **4l** | 3 | 273.033 | −0.395 | 0.157 | −3.63 | −4.769 | 65.812 |
| **4m** | 3 | 263.264 | −0.176 | 0.256 | −3.663 | −5.283 | 57.592 |
| **4n** | 3 | 262.929 | −0.359 | 0.299 | −3.67 | −5.12 | 57.61 |
| **4o** | 3 | 80.252 | −0.906 | −0.038 | −3.61 | −4.248 | 80.104 |
| **4p** | 3 | 263.137 | −0.223 | 0.181 | −3.608 | −4.907 | 57.613 |
| Amp[h] | 1 | 1.298 | −1.3 | −0.929 | −0.709 | −1.512 | 139.52 |
| Quin[h] | 3 | 633.127 | 0.1 | 0.26 | −5.518 | −3.306 | 46.551 |
| CQ[h] | 3 | 1486.183 | 0.411 | 0.631 | −6.484 | −4.758 | 26.686 |

[a]Percentage human oral absorption (>80% high to <25% poor).
[b]caco-2 cell permeability (<25 poor to >500 great).
[c]Blood brain partition coefficient (−3.0 to 1.2).
[d]Prediction of binding to human serum albumin (−1.5 to 1.5).
[e]Predicted IC50 value for blockage of HERG $K^+$ channels (below −5.0).
[f]Water solubility parameter (−6.5 to 0.5).
[g]van der Walls surface area of polar nitrogen and oxygen atoms (7.0-200.0).
[h]Standard drugs.

phenyl interacts with ASP 73 (2.21 Å), ASP 73 (2.86 Å), —CO-ARG 76 (2.37 Å), and —$OCH_3$-GLY 101 (2.31 Å) in *4UDH* protein. Compound **4c** (XP GScore −2.41) has three strong H-bonds between quinoline-C-LYS 273 (2.53 Å), —$OCH_3$ interact with LYS 316 (2.02 Å) and LYS 316 (2.57 Å), compound **4p** (XP GScore −4.535) found four H-bonds between quinoline-C-ASN 104 (2.34 Å), —CO interact with LYS 273 (1.85 Å), LYS 273 (4.25 Å), and LYS 316 (1.58 Å) in *4CJN* protein. Compound **4c** (XP GScore −6.157) generates four H-bonds between —$CH_3$-ASN 144 (2.55 Å), —CO interact with ARG 129 (1.85 Å), SER 128 (2.69 Å), and ARG 106 (1.85 Å); compound **4d** (XP GScore −7.059) generates one halogen bond and four H-bonds between —Cl-ASN 144 (3.37 Å), —CO interact with ARG 129 (1.85 Å), ARG 106 (3.11 Å), ARG 106 (1.90 Å), and ARG 106 (2.32) in *1J3J* protein. Moreover, compounds **4c**, **4d**, and **4p** having good binding score as compared to standard drugs ampicillin (*4DUH*: −3.65, *4CJN*: −6.721), ciprofloxacin (*4DUH*: −4.051, *4CJN*: −3.973), quinine (*1J3J*: −4.878), and chloroquine (*1J3J*: −4.915). Furthermore, compounds **4o** (XP GScore −5.141), **4j** (XP GScore −2.242), and **4i** XP GScore (−5.666) having very low binding score with proteins *4DUH*, *4CJN,* and *1J3J*, respectively. Docking score and binding mechanism of all compounds suggested that highlighted compounds would be a potent active in the respective protein as described in Table 6.

## 3.5 | ADME-Tox prediction

ADME-Tox properties were evaluated for all synthesized compounds for their in silico pharmacophore and drug likeness properties via QikPro tool (Schrodinger, LLC, New York, NY, 2015). Drug likeness properties of all evaluated molecules results were described with their acceptable range in Table 7. The predicted results were compared with the acceptable range between >80% high to <25% poor for percentage human oral absorption (PHOA), <25 poor to >500 great for caco-2

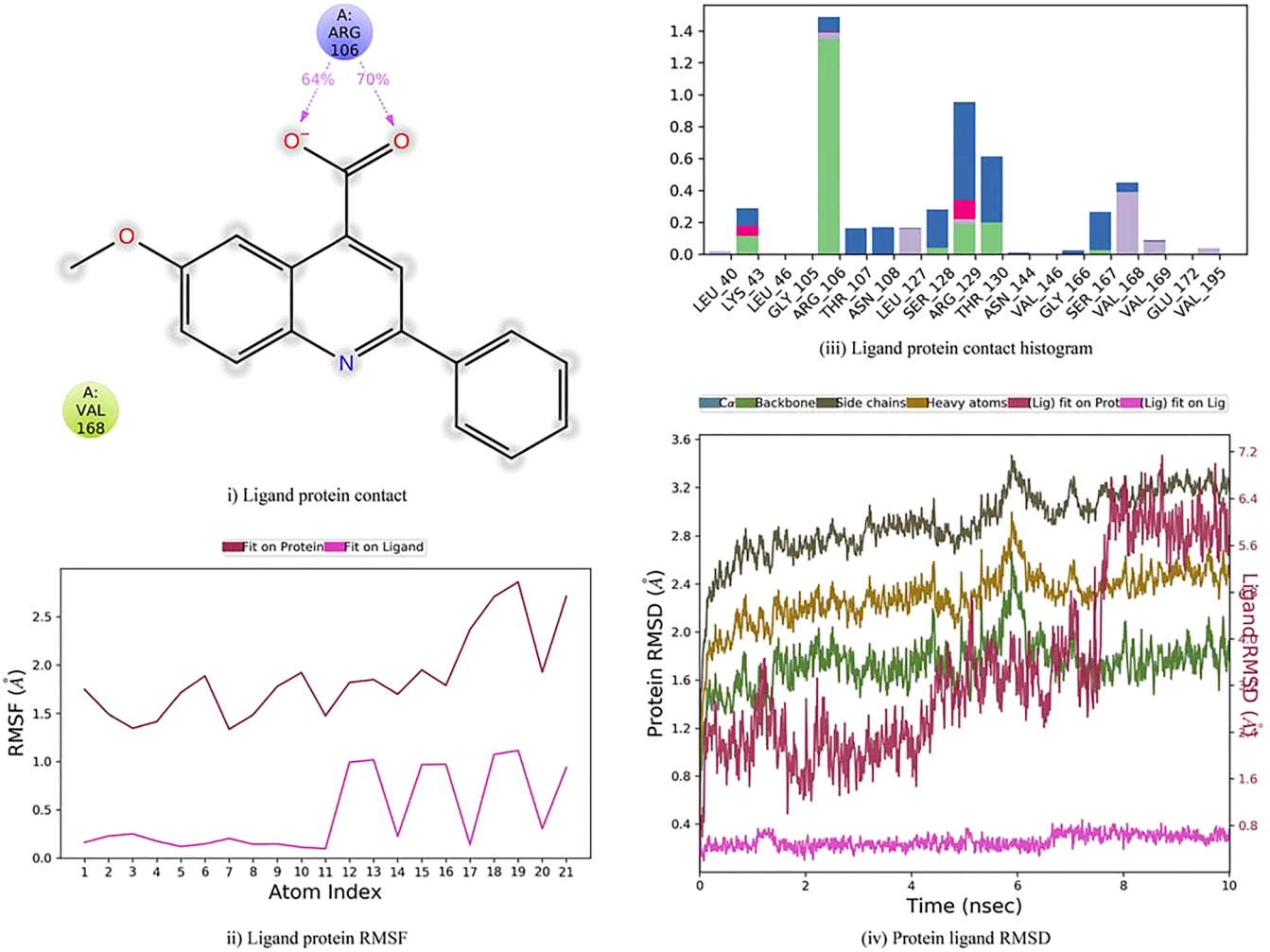



**FIGURE 5** Molecular dynamics simulation diagram of compound **4c** with PDB: 1J3J. A, Ligand protein contact. B, Ligand protein RMSF. C, Ligand protein contact histogram. D, Protein ligand RMSD [Color figure can be viewed at wileyonlinelibrary.com]

cell permeability (QPPCaco), −3.0 to 1.2 for blood-brain partition coefficient (QPlogBB), −1.5 to 1.5 for prediction of binding to human serum albumin (QPlogKhsa), below −5.0 for predicted IC50 value for blockage of HERG $K^+$ channels (QPlogHERG), −6.5 to 0.5 for water solubility parameter (QPlogS), 7.0 to 200.0 for van der Walls surface area of polar nitrogen and oxygen atoms (PSA). All synthesized compounds were found to be satisfactory results for pharmacophore properties. Among all the compounds, the selected compounds **4a**, **4c**, **4d**, **4l**, and **4p** have a higher biological activity and an acceptable range of ADME-Tox. We stated that the selected compounds should be promising considering the future scope.

## 3.6 | Molecular dynamics

In the MD study, best-docked compound **4c** was selected with PDB: *1J3J* for their simulation study. Ten-nanosecond (10 000 ps) simulation running time was selected for ligand complex study. The simulation trajectory was analyzed every 1 ns with the best binding pose from calculated RMSD (Å) value. MD suggested that protein residues *LYS 43*, *ARG 106*, *SER 128*, *ARG 129*, *THR 130*, and *SER 167* interact with hydrogen during the simulation. Various energies, ligand properties, and ligand interactions were noted in the study. According to the study, we have found that compound **4c** was fluctuated at 2.8 Å with carboxylic group and the ligand was stabilized in the fluctuation range 1.3 to 2.8 Å. Here, ligand-protein showed their inhibitor bound and open catalytic activity side with ARG 106. MD and other descriptions are described in Figure 5.

## 4 | CONCLUSION

In summary, we have established a green and highly efficient one-pot three-component microwave irradiation

protocol for the synthesis of various quinoline-4-carboxylic acids catalyzed by *p*-toluenesulfonic acid. The *p*-TSA catalyst was easily commercially available and nonhazardous. There are many features of this protocol, including high yield of products with high purity as well as lower reaction time compared with conventional methods, a simple work-up process and avoidance of the use of hazardous organic solvents. A simple work-up procedure makes the present method a valuable contribution in agreement with green chemistry principles. We have synthesized compounds **4a-4p** and tested their biological activity. Compounds **4a**, **4c**, **4d**, and **4n** were found to be most active in *E. coli*; compounds **4c** and **4p** were found to be active in *S. aureus*; and compounds **4c** and **4d** were found active in *P. falciparum* strain. Molecular docking study was suggested that synthesized compounds were fit into the active site of protein and predict best mechanism of in silico side. Best dock compound **4c** was selected for the MD. ADME-Tox and MD studies were used for the implementing the new drug development and to understand the in silico behavior of compounds.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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