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Design, Synthesis, SAR, Pharmacokinetic Prediction of New 4-Quinolones as Anti-Microbial Agents

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Abstract – A series of new 4-quinolone derivatives was synthesized by conventional heating method. For the synthesized compounds, we performed pharmacokinetic prediction, SAR and antimicrobial assay. The presence of halogen elements plays a key role in the biological activity that is clear by *in vitro* analysis. Target compounds exhibit moderate to significant activity near to standard marketed drugs like amoxycillin, chloramphenicol, ciprofloxacin, norfloxacin, griseofulvin, and nystatin.

Keywords: 4-quinolone, anti-microbial activity, SAR, pharmacokinetic prediction, Swiss ADME, drug likeness

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INTRODUCTION

The treatment of many infectious diseases remains a challenging task in the current scenario because of the combination of factors such as the alarming increase in several multi-drug-resistant microbial pathogens and the advent of newer infectious diseases such as severe acute respiratory syndrome, and avian influenza. Despite the availability of many antibiotics and chemotherapeutics, the increasing clinical importance of drug-resistant microbial pathogens has lent additional urgency to microbiological and antifungal research [1–4]. During the last few decades, attention has been given to the synthesis of chloro- and flouro-substituted quinolones such as norfloxacin, ofloxacin, enoxacin, enrofloxacin, ciprofloxacin, etc. as potential antibacterial agents (Scheme 1) [5]. Diethyl 2-(ethoxymethylene)malonate is widely used in the push-pull alkene [6], 1,4-addition-elimination [7], cycloaddition, and protection group of amino acid [8]. Many chloro- and flouroquinolones have been synthesized via Gould Jacob reaction using diethyl 2-(ethoxymethylene)malonate [9, 10].

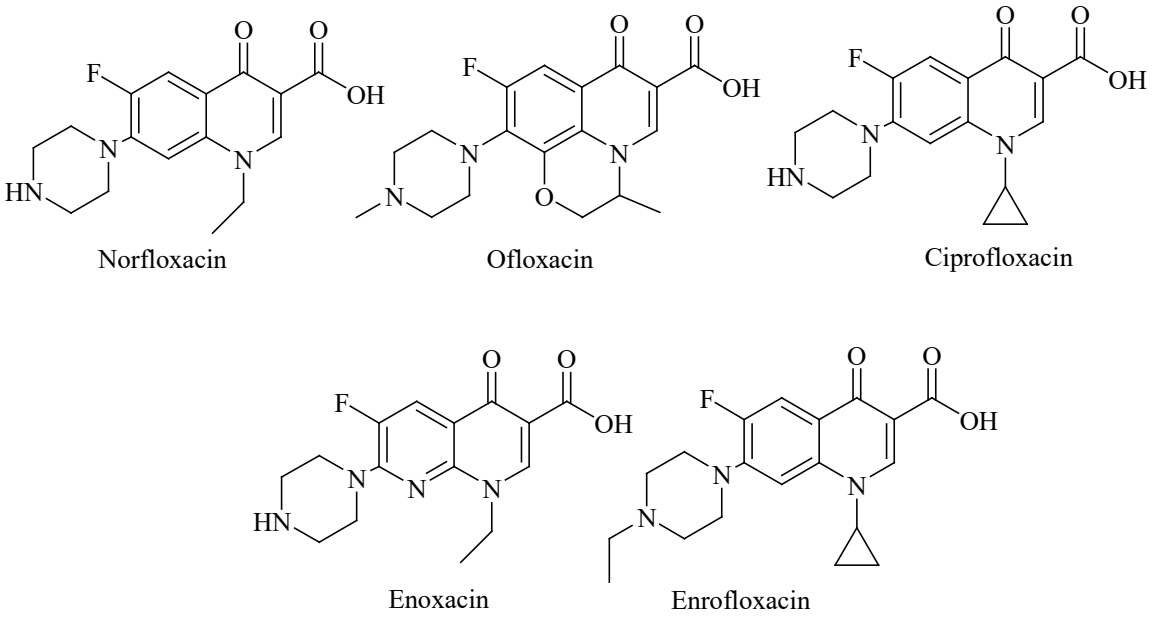
Recent studies show that 4-quinolone [11] are characterized as broad-spectrum antibacterial drugs active against both Gram-positive and Gram-negative bacteria. Besides broad-spectrum activity, the success of fluoroquinolones can be attributed to their properties such as good bioavailability after oral administration, relatively low toxicity, and favourable pharmacokinetics [12]. The influence of lipophilicity and toxicity study [13] of molecules in the drug design process plays a key role in drug designing. An increase in the lipophilic chain is a key factor to improve the bioavailability of molecules in the body protein. Mainly our focus and contribution to medicinal chemistry are to design and develop antidiabetic, anticancer, antioxidant, and antimicrobial agents [14–21].

RESULTS AND DISCUSSION

In the current work, we synthesized 4-quinolone derivatives (Scheme 2). Synthesis of 4-quinolones done by Gould Jacob reaction the reaction of aromatic amines with diethyl 2-(ethoxymethylene)malonate. The synthesized 4-quinolone compounds **3a**–**3j** are the intermediates for the final series of compounds. The intermediate compounds **3a**–**3j** further reacted with 1-bromopropane to yield an *N*-propylated final products **4a**–**4j**.

All the synthesized compounds were evaluated for *in vitro* anti-microbial assay as standard protocol described in experimental section. For the anti-microbial assay the strain utilized *Staphylococcus aureus* (MTCC-96),

Scheme 1.



Scheme 2.

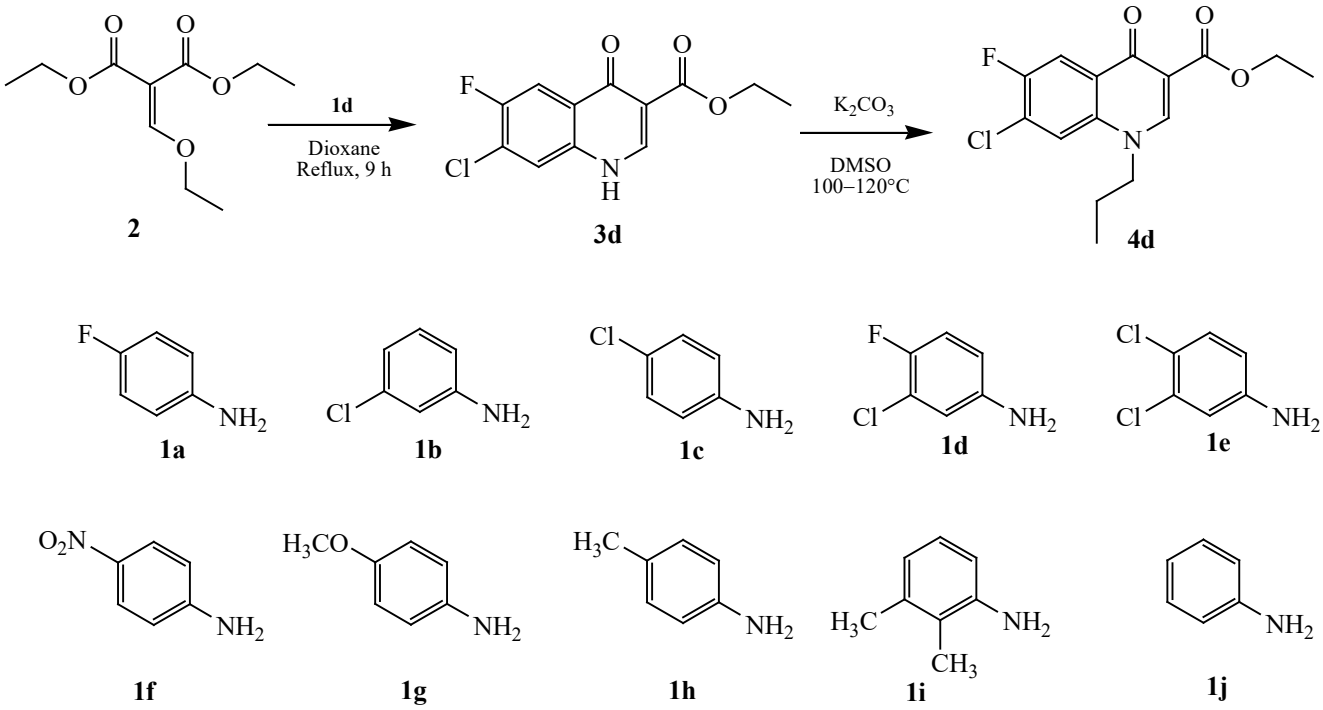


Table 1. Comparative antimicrobial activity for the MIC of synthesized compounds and standard drug

Compound	Minimum inhibition concentration, μg/mL						
	gram-positive bacteria		gram-negative bacteria		fungal species		
	Staphylococcus aureus (MTCC-96)	*Streptococcus pyogenes* (MTCC 443)	*Escherichia coli* (MTCC 442)	*Pseudomonas aeruginosa* (MTCC 441)	*Candida albicans* (MTCC 227)	*Aspergillus niger* (MTCC 282)	*Aspergillus clavatus* (MTCC 1323)
4a	100	100	500	100	500	125	250
4b	150	150	100	100	250	125	250
4c	100	100	200	150	200	200	250
4d	100	125	62.5	125	150	125	125
4e	100	100	250	500	1000	500	250
4f	500	500	250	125	>1000	500	1000
4g	500	250	250	250	1000	500	500
4h	1000	250	500	500	1000	500	250
4i	200	250	250	200	500	500	250
4j	250	250	250	500	500	500	250
Ampicillin	250	100	100	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	50	50	25	25	–	–	–
Norfloxacin	10	10	10	10	–	–	–
Nystatin	–	–	–	–	100	100	100
Griseofulvin	–	–	–	–	500	100	100

Streptococcus pyogenes (MTCC 443) as gram positive bacteria; *Escherichia coli* (MTCC 442), *Pseudomonas aeruginosa* (MTCC 441) as gram negative bacteria and *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282), *Aspergillus clavatus* (MTCC 1323) as fungal strain. Some compounds show good MIC values as compared with standard drugs. The results are depicted in Table 1.

Drug-likeness and pharmacokinetic (ADME) prediction. The Swiss-ADME software (http://www.swissadme.ch) was an online tool for determining the drug-likeness and pharmacokinetic parameters of the proposed derivatives. Using Lipinski's rule of 5, the drug-likeness of the compounds was predicted. The guideline was created to establish ground rules for new molecular entities in terms of drug-likeness [22]. According to the rule of 5, molecules having H-bond donors greater than 5, H-bond acceptors greater than 10, a molecular weight larger than 500, and log *P* (iLog *P*) larger than 5. Other parameters like topological polar surface area (TPSA) for **4d** is 48.3 Å^2 < 140 Å^2 and the number of rotatable bonds (nRotb) was reported [23] to have poor absorption. The pharmacokinetic properties to be determined include the molar refractivity (MR), log of skin permeability (log K_p), blood-brain barrier (BBB) penetration, permeability glycoprotein (Pgp) substrate, gastrointestinal (GI) absorption, and cytochrome P450 (CYP450) enzymes CYP1A2, CYP2C9, and CYP2C19 inhibitors.

The above study suggests that our compound **4d** is less toxic from the data of all log*P* values and TPSA value 48.3 Å^2 shows very little toxicity in process of drug design. The Lipinski violation is also zero that is also a good sign our molecule. Bioavailability score is 0.55 is suggesting that molecule can be easily bioavailable in the body. Finally, the predicted medicinal study clearly indicates that the molecule itself possess lead likeness which is clear indication of drug likeness.

SAR discussion. SAR is the key factor in process of drug designing. From results of MIC values for anti-microbial assay it is clear visible relation of halogenated

compounds **4a**–**4e** show moderate to good activities. While in comparison with compounds **4f**–**4j** alkyl and methoxy substituted compounds are comparatively less active than the halogenated compound for the anti-microbial assay. In process of drug designing for the anti-microbial compounds the halogenated compounds are preferred over other alkyl or other substitution.

EXPERIMENTAL

All chemicals, solvents, and media were purchased from Sigma Aldrich, Combi-Block, Enamine, Himedia, and SRL. All purchased chemicals were used without further purification, and reactions were continuously monitored by thin layer chromatography (TLC) on silica gel G60 F254 (Merck) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or with iodine vapor or aq. KMnO4. Melting points were determined using a Buchi B-540 capillary apparatus. NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) in DMSO-d_6, and chemical shifts are referenced to the solvent residual signals concerning tetramethylsilane. The control of reaction temperature was monitored by a ruby thermometer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70eV) model using a direct inlet probe technique and m/z is reported in atomic units per elementary charge.

General procedure for synthesis of intermediates 3a–3j. A mixture of aniline **1** (0.01 mol) and diethyl 2-(ethoxymethylene)malonate (0.1 mol) was taken in 20 mL of dioxane and heated and stirred at reflux for 9 h. The reaction mixture was allowed to cool at room temperature and poured in ice-cooled water. The precipitated product dried under a vacuum and recrystallized from absolute alcohol.

Ethyl 6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (3a). Yield 64%, off white powder, mp 92–94°C. ^{1}H NMR spectrum, δ, ppm: 8.84 s (1H, NCH), 6.75–7.26 m (3H, CH_{Ar}), 4.29 q (2H, J = 5.0 Hz, OCH_2), 4.09 s (1H, NH), 1.35 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 61.0, 110.2, 113.4, 117.6, 130.4, 122.3, 135.6, 147.2, 158.5, 165.3 (>C=O_{ester}), 176.1 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 235. Found, %: C 61.29; H 4.28; F 8.07; N 5.96. $C_{12}H_{10}FNO_3$. Calculated, % C, 61.28; H, 4.29; F, 8.08; N, 5.95.

Ethyl 7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3b). Yield 59%, white powder, mp 83–85°C. ^{1}H NMR spectrum, δ, ppm: 8.82 s (1H, NCH), 7.34–7.96 m (3H, CH_{Ar}), 4.23 q (2H, J = 7.5 Hz, OCH_2), 4.11 s (1H, NH), 1.31 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 61.4, 112.5, 115.7, 127.3, 128.1, 129.4, 144.4, 147.3, 150.2, 164.8 (>C=O_{ester}), 176.7 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 251. Found, %: C 57.29; H 4.00; Cl 14.08; N 5.57. $C_{12}H_{10}NO_3Cl$. Calculated, %: C 57.27; H 4.01; Cl 14.09; N 5.57.

Ethyl 6-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3c). Yield 72%, white powder, mp 88–90°C. ^{1}H NMR spectrum, δ, ppm: 8.85 s (1H, $CH_{quinolone}$), 7.69–6.72 m (3H, CH_{Ar}), 4.21 q (2H, J = 7.5 Hz, OCH_2), 4.08 s (1H, NH), 1.29 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 61.4, 112.5, 115.7, 127.1, 128.3, 129.5, 144.2, 147.2, 150.2, 164.8 (>C=O_{ester}), 176.7 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 251. Found, %: C 57.29; H 4.01; Cl 14.07; N 5.58. $C_{12}H_{10}NO_3Cl$. Calculated, %: C 57.27; H 4.01; Cl 14.09; N 5.57.

Ethyl 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3d). Yield 55%, white powder, mp 109–111°C. ^{1}H NMR spectrum, δ, ppm: 8.82 s (1H, NCH), 7.24–6.90 m (2H, CH_{Ar}), 4.23 q (2H, J = 8.0 Hz, CH_2), 4.12 s (1H, NH), 1.35 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.2, 64.3, 112.3, 114.5, 118.8, 127.3, 129.6, 145.8, 147.2, 157.3, 165.1 (>C=O_{ester}), 176.3 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 269. Found, %: C 53.45; H 3.37; Cl 13.14; F 7.06; N 5.18. $C_{12}H_9NO_3ClF$. Calculated, %: C 53.45; H 3.36; Cl 13.15; F 7.05; N 5.19.

Ethyl 6,7-dichloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3e). Yield 63%, white powder, mp 96–98°C. ^{1}H NMR spectrum, δ, ppm: 8.93 s (1H, NCH), 7.64–6.95 m (2H, CH_{Ar}), 4.23 q (2H, J = 8.0 Hz, CH_2), 4.09 s (1H, NH), 1.26 t (3H, J = 8.0 Hz, CH_3), ^{13}C NMR spectrum, δ_C, ppm: 12.3, 61.2, 112.3, 118.6, 129.4, 131.7, 137.6, 147.7, 148.2, 148.3, 165.3 (>C=O_{ester}), 176.4 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 286. Found, %: C 50.39; H 3.16; Cl 24.76; N 4.92. $C_{12}H_9Cl_2NO_3$. Calculated, %: C 50.38; H 3.17; Cl 24.78; N 4.90.

Ethyl 6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3f). Yield 47%, yellowish powder, mp 100–102°C. ^{1}H NMR spectrum, δ, ppm: 8.97 s (1H, NCH), 7.82–6.89 m (3H, CH_{Ar}), 4.23 q (2H, J = 8.2 Hz, CH_2), 4.06 s (1H, NH), 1.29 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.5, 61.2, 112.2, 112.3, 117.7, 124.3, 130.7, 138.4, 146.2, 147.7, 165.3 (>C=O_{ester}), 176.2 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 262. Found, %: C 54.98; H 3.85; N 10.66. $C_{12}H_{10}N_2O_5$. Calculated, %: C 54.97; H 3.84; N 10.68.

Ethyl 6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (3g). Yield 62%, white powder, mp 86–88°C. ^{1}H NMR spectrum, δ, ppm: 8.83 (s, 1H, NCH), 7.70–7.52 m (3H, CH_{Ar}), 4.20 q (2H, J = 8.0 Hz, CH_2), 4.05 s (1H, NH), 3.96 s (3H, OCH_3), 1.26 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 55.8, 61.2, 112.2, 112.3, 117.2, 120.9, 130.7, 132.4, 147.7, 155.3, 165.0 (>C=O_{ester}), 176.5 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 247. Found, %: C 63.16; H 5.30; N 5.66. $C_{13}H_{13}NO_4$. Calculated, %: C 63.15; H 5.30; N 5.67.

Ethyl 6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3h). Yield 66%, white powder, mp 87–99°C. ^{1}H NMR spectrum, δ, ppm: 8.84 s (1H, NCH), 7.79–6.92 m (3H, CH_{Ar}), 4.23 q (2H, J = 8.2 Hz, OCH_2), 4.04 s (1H, NH), 3.96 s (3H, Ar-CH_3), 1.27 t (3H, J = 8.2 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 61.2, 112.2, 112.4, 116.7, 124.5, 129.9, 131.8, 135.6, 137.1, 147.7, 165.1 (>C=O_{ester}), 176.3 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 231. Found, %: C 67.51; H 5.66; N 6.08. $C_{13}H_{13}NO_3$. Calculated, %: C 67.52; H 5.67; N 6.06.

Ethyl 7,8-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3i). Yield 63%, white powder, mp 68–70°C. ^{1}H NMR spectrum, δ, ppm: 8.87 s (1H, NCH), 7.58–6.84 m (2H, CH_{Ar}), 4.38 q (2H, J = 8.0 Hz, OCH_2), 4.01 s (1H, NH), 2.36 s (3H, Ar-CH_3), 2.14 s (3H, Ar-CH_3), 1.36 t (3H, J = 8.0 Hz, CH_3), ^{13}C NMR spectrum, δ_C, ppm: 13.8, 14.3, 61.2, 122.6, 122.6, 123.2, 126.8, 139.2, 144.9, 147.7, 165.3 (>C=O_{ester}), 176.1 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 245. Found, %: C 68.56; H 6.15; N 5.72. $C_{14}H_{15}NO_3$. Calculated, %: C 68.56; H 6.16; N 5.71.

Ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (3j). Yield 71%, white powder, mp 116–118°C. ^{1}H NMR spectrum, δ, ppm: 8.89 s (1H, NCH), 7.86 d (1H, J = 7.5 Hz, CH_{Ar}), 7.64 t (1H, J = 8.2 Hz, CH_{Ar}), 6.93 t (1H, J = 5.6 Hz, CH_{Ar}), 6.73 d (1H, J = 7.5 Hz, CH_{Ar}), 4.24 q (2H, J = 8.0 Hz, OCH_2), 4.11 s (1H, NH), 1.30 t (3H, J = 8.0 Hz, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.2, 61.5, 112.1, 118.3, 124.3, 126.3, 129.9, 135.3, 140.1, 147.7, 165.1 (>C=O_{ester}), 176.4 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 217; Found, %: C 66.36; H 5.11; N 6.47. $C_{12}H_{11}NO_3$. Calculated, %: C 66.35; H 5.10; N 6.45.

General procedure for synthesis of compounds 4a–4j. A mixture of intermediate **3** (0.01 mol) and potassium carbonate (0.02 mol), in dimethyl sulfoxide (20 mL) was heated and stirred at 110–120°C for 1 h and then allowed to cool up to 50–55°C. To this reaction mixture, the solution of 1-bromopropane (0.01 mol) in dimethyl sulfoxide (6 mL) was added dropwise and the temperature was maintained 95–100°C for 8 h. The resulting mixture was poured onto crushed ice, filtered, washed with water, and dried under vacuum. The product was recrystallized from ethanol.

Ethyl 6-fluoro-1-*N*-propyl-1,4-dihydroquinoline-4-one-3-carboxylate (4a). Yield 52%, off white powder, mp 82–84°C. ^{1}H NMR spectrum, δ, ppm: 9.06 s (1H, NCH), 6.75–7.26 m (3H, CH_{Ar}), 4.29 q (2H, J = 8.0 Hz, OCH_2), 4.09 q (2H, J = 7.1 Hz, NCH_2), 1.9 m (2H, NCH_2CH_2), 1.35 t (3H, J = 8.0. Hz, Et-CH_3), 0.94 t (3H, J = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.2, 14.3, 21.3, 51.1, 61.0, 110.2, 113.5, 117.3, 122.4, 130.4, 134.6, 146.2, 157.5, 165.0 (>C=O_{ester}), 171.1 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 277. Found, %: C 64.96; H 5.83; F 6.86; N 5.04. $C_{15}H_{16}NO_3F$. Calculated, %: C 64.97; H 5.82; F 6.85; N 5.05.

Ethyl 7-chloro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4b). Yield 54%, Dirty white powder, mp 74–76°C. ^{1}H NMR spectrum, δ, ppm: 9.05 s (1H, NCH), 8.10–7.34 m (3H, CH_{Ar}), 4.23 q (2H, J = 8.0 Hz, OCH_2), 4.12 q (2H, J = 7.1 Hz, NCH_2), 1.72 m (2H, NCH_2CH_2), 1.31 t (3H, J = 8.0 Hz, Et-CH_3), 0.91 t (3H, J = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.8, 14.4, 21.1, 51.2, 61.4, 110.1, 116.5, 125.7, 127.4, 130.1, 139.4, 141.1, 146.3, 165.2 (>C=O_{ester}), 172.7 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 293. Found, %: C 61.33; H 5.47; Cl 12.08; N 4.78. $C_{15}H_{16}NO_3Cl$. Calculated, %: C 61.33; H 5.49; Cl 12.07; N 4.77.

Ethyl 6-chloro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4c). Yield 55%, white powder, mp 85–87°C. ^{1}H NMR spectrum, δ, ppm: 9.01 s (1H, NCH), 7.69–6.72 m (3H, CH_{Ar}), 4.20 q (2H, J = 8.2 Hz, OCH_2), 4.08 q (2H, J = 7.1 Hz, NCH_2), 1.74 m (2H, NCH_2CH_2), 1.29 t (3H, J = 8.0 Hz, Et-CH_3), 0.90 t (3H, J = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.9, 14.2, 21.1, 51.0, 61.8, 110.1, 116.4, 127.5, 131.1, 135.4, 137.2, 146.1, 165.0 (>C=O_{ester}), 172.3 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 293. Found, %: C, 61.34; H, 5.46; Cl, 12.08; N, 4.78. $C_{15}H_{16}NO_3Cl$. Calculated, %: C, 61.33; H, 5.49; Cl, 12.07; N, 4.77.

Ethyl 7-chloro-6-fluoro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4d). Yield 47%, white powder, mp 101–103°C. ^{1}H NMR spectrum, δ, ppm: 9.05 s (1H, NCH), 7.19–6.96 m (2H, CH_{Ar}), 4.21 q (2H, J = 8.0 Hz, OCH_2), 4.07 q (2H, J = 7.1 Hz, NCH_2), 1.70 m (2H, NCH_2CH_2), 1.31 t (3H, J = 8.0 Hz, Et-CH_3), 0.94 t (3H, J = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.9, 14.2, 21.0, 51.0, 110.2, 114.4, 118.2, 127.3,

128.7, 135.2, 146.1, 155.2, 165.2 (>C=O_{ester}), 171.3 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 312. Found, %: C 57.76; H 4.86; Cl 11.38; F 6.09; N 4.50. $C_{15}H_{15}ClFNO_3$. Calculated, %: C, 57.79; H, 4.85; Cl, 11.37; F, 6.09; N, 4.49.

Ethyl 6,7-dichloro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4e). Yield 49%, white powder, mp 90–92°C. ^{1}H NMR spectrum, δ, ppm: 9.07 s (1H, NCH), 7.53–6.91 m (2H, CH_{Ar}), 4.20 q (2H, *J* = 8.0 Hz, OCH_2), 4.09 q (2H, *J* = 7.1 Hz, NCH_2), 1.79 m (2H, NCH_2CH_2), 1.29 t (3H, *J* = 8.0 Hz, Et-CH_3), 0.90 t (3H, *J* = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.9, 14.2, 21.0, 51.0, 110.2, 114.4, 118.2, 127.3, 128.7, 135.2, 146.1, 155.2, 165.2 (>C=O_{ester}), 171.3 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 328. Found, %: C 57.76; H 4.86; Cl 11.38; F 6.09; N 4.50. $C_{15}H_{15}ClFNO_3$. Calculated, %: C 57.79; H 4.85; Cl 11.37; F 6.09; N 4.49.

Ethyl 6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4f). Yield 49%, light yellowish powder, mp 97–99°C. ^{1}H NMR spectrum, δ, ppm: 9.05 s (1H, NCH), 8.32–7.01 m (3H, CH_{Ar}), 4.23 q (2H, *J* = 8.0 Hz, OCH_2), 4.07 q (2H, *J* = 7.2 Hz, NCH_2), 1.70 m (2H, NCH_2CH_2), 1.27 t (3H, *J* = 8.0 Hz, Et-CH_3), 0.95 t (3H, *J* = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 12.0, 14.7, 21.3, 51.2, 61.1, 107.2, 110.4, 124.2, 128.3, 136.7, 138.2, 145.1, 146.2, 146.2, 165.0 (>C=O_{ester}), 176.3 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 304. Found, %: C 59.22; H 5.28; N 9.22. $C_{15}H_{16}N_2O_5$; Calculated, %: C 59.21; H 5.30; N 9.21.

Ethyl 6-methoxy-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4g). Yield 50%, white powder, mp 77–79°C. ^{1}H NMR spectrum, δ, ppm: 9.07 s (1H, NCH), 7.70–7.52 m (3H, CH_{Ar}), 4.20 q (2H, *J* = 8.0 Hz, OCH_2), 4.04 q (2H, *J* = 7.1 Hz, NCH_2), 3.96 s (3H, Ar-OCH_3), 1.71 m (2H, NCH_2CH_2), 1.29 t (3H, *J* = 8.0 Hz, Et-CH_3), 0.93 t (3H, *J* = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.9, 14.3, 21.2, 51.3, 55.8, 61.4, 105.5, 110.6, 112.2, 120.3, 130.1, 131.2, 146.3, 153.7, 165.6 (>C=O_{ester}), 171.9 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 289. Found, %: C 66.42; H 6.62; N 4.84. $C_{16}H_{19}NO_4$. Calculated, %: C 66.43; H 6.61; N 4.84.

Ethyl 6-methyl-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4h). Yield 50%, white powder, mp 77–79°C. ^{1}H NMR spectrum, δ, ppm: 9.07 s (1H, NCH), 7.70–7.52 m (3H, CH_{Ar}), 4.20 q (2H, *J* = 8.0. Hz, OCH_2), 4.04 q (2H, *J* = 8.0 Hz, NCH_2), 3.96 s (3H, Ar-CH_3), 1.71 m (2H, NCH_2CH_2), 1.29 t (3H, *J* = 8.0 Hz, Et-CH_3), 0.93 t (3H, *J* = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.9, 14.3, 21.2, 51.3, 55.8, 61.4, 105.5, 110.6, 112.2, 120.3, 130.1, 131.2, 146.3, 153.7, 165.6 (>C=O_{ester}), 171.9 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 289. Found, %: C 66.42; H 6.62; N 4.84. $C_{16}H_{19}NO_4$. Calculated, %: C 66.43; H 6.61; N 4.84.

Ethyl 7,8-dimethyl-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4i). Yield 58%, white powder, mp 58–60°C. ^{1}H NMR spectrum, δ, ppm: 9.06 s (1H, NCH), 7.38–6.74 m (2H, CH_{Ar}), 4.34 q (2H, *J* = 8.2 Hz, OCH_2), 4.03 q (2H, *J* = 7.3 Hz, NCH_2), 2.34 s (3H, Ar-CH_3), 2.12 s (3H, Ar-CH_3), 1.74 m (2H, NCH_2CH_2), 1.32 t (3H, *J* = 8.0 Hz, Et-CH_3), 0.91 t (3H, *J* = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 11.4, 13.7, 14.5, 18.3, 21.3, 51.5, 61.1, 110.2, 120.3, 121.1, 122.6, 143.4, 165.7 (>C=O_{ester}), 176.5 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 287. Found, %: C 71.05; H 7.38; N 4.87. $C_{17}H_{21}NO_3$. Calculated, %: C 71.06; H 7.37; N 4.87.

Ethyl 4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (4j). Yield 51%, white powder, mp 110–112°C. ^{1}H NMR spectrum, δ, ppm: 9.04 s (1H, NCH), 7.84 d (1H, *J* = 8.2 Hz, CH_{Ar}), 7.54 t (1H, *J* = 7.5 Hz, CH_{Ar}), 6.99 t (1H, *J* = 1.5 Hz, CH_{Ar}), 6.71 d (1H, *J* = 7.5 Hz, CH_{Ar}), 4.24 q (2H, *J* = 8.0 Hz, OCH_2), 4.11 q (2H, *J* = 7.1 Hz, NCH_2), 1.71 m (2H, NCH_2CH_2), 1.30 t (3H, *J* = 8.0 Hz, Et-CH_3), 0.92 t (3H, *J* = 8.0 Hz, Pr-CH_3). ^{13}C NMR spectrum, δ_C, ppm: 12.7, 14.1, 21.4, 51.2, 61.3, 110.1, 116.7, 122.1, 129.0, 135.0, 139.1, 146.3, 165.3 (>C=O_{ester}), 172.4 (>C=$O_{quinolone}$). Mass spectrum (EI), *m/z*: 259. Found, %: C 69.48; H 6.60; N 5.41. $C_{15}H_{17}NO_3$. Calculated, %: C 69.48; H 6.61; N 5.40.

***In vitro* antimicrobial assay.** All MTCC cultures were collected from the Institute of Microbial Technology, Chandigarh. The MICs of synthesized compounds were carried out by broth microdilution method against the standard bacterial strains *S. aureus* MTCC 96, *S. pyogenes* MTCC 442, *E. coli* MTCC 443, and *P. aeruginosa* MTCC 1688 and antifungal activity against the standard fungal strains *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323. DMSO was used a sdiluents to get desired concentration of compounds to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub-cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the

accuracy of the compound concentrations. The MIC was defined as the lowest concentration of the antibiotic or test sample allowing no visible growth. All the tubes showing no visible growth (same as the control tube) were subcultured and incubated overnight at 37°C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show a similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized compound was diluted obtaining 2000 mg/mL concentration as a stock solution. In primary screening 500, 250, and 200 mg/mL concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in the second set of dilutions against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 100, 62.5, 50, and 25 mg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

CONCLUSIONS

In this study, we synthesized total 20 molecules including 10 intermediates (**3a**–**3j**) and 10 final compounds (**4a**–**4j**). All the synthesized compounds are screened for anti-microbial assay for the MIC. All data compare with amoxycillin, chloramphenicol, ciprofloxacin, norfloxacin, griseofulvin, nystatin as standard drugs. The results indicate the higher activity of compound **4d** and moderate activity of **4a**, **4b**, **4c**, and **4e**. The SAR and pharmacokinetic study are represented about the most active compound. The lipophilicity, toxicity, and other parameters are also discussed. From the result we conclude that the designing of halogenated compounds will be more favourable in comparison of other substitution.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

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