European Journal of Chemistry

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Synthesis, antimicrobial, antioxidant, and ADMET studies of quinoline derivatives

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RESEARCH ARTICLE

10.5155/eurjchem.12.1.37-44.2038

Received: 31 August 2020
Received in revised form: 10 January 2021
Accepted: 15 January 2021
Published online: 31 March 2021
Printed: 31 March 2021

KEYWORDS

DPPH
ADMET
Acetohydrazide
Antioxidant activity
Antimicrobial activity
2-Chloroquinoline-3-carbaldehyde

ABSTRACT

The synthesis, antimicrobial, and antioxidant activities of new quinoline analogs were carried out with the aim to find possible hits/leads that can be taken up for future drug development. A series of 2-amino-*N*'-((2-chloroquinolin-3-*yl*)methylene)acetohydrazide derivatives (6a-h) have been synthesized by reacting 2-chloro-*N*'-((2-chloroquinolin-3-yl)methylene)acetohydrazide (5a) and *N*'-((6-bromo-2-chloroquinolin-3-yl)methylene)-2-chloroacetohydrazide (5b) with secondary amines (Morpholine, diethylamine, piperidine and 1-methylpiperazine). The characterization was achieved by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis. The *in silico* ADMET studies of the synthesized molecules were analyzed for their drug likeliness and toxic properties. The ADMET study indicates that the synthesized compounds were found to be possessing reliable ADME properties and are nontoxic. The antimicrobial properties were tested against bacterial and fungal species with amoxicillin and fluconazole as standard drugs. The compounds 6a, 6c, 6e, and 6g exhibited good antibacterial potency against *P. aeruginosa,* and the compounds 6a, 6f, and 6h have shown good activity against *E. coli* with 1000 µg/mL. The compounds 6b, 6c, and 6e have moderate activity against fungal species *C. oxysporum* and the compounds 6c, 6e, 6f, 6g, and 6h have good activity against *P. chrysogenum*. Synthesized compounds were also tested for the DPPH· free radical scavenging activity to check the antioxidant potential, and the results revealed that the compounds 6a, 6b, 6c, and 6e have exhibited antioxidant potency than the remaining synthesized derivatives. The possible hits generated from biological activity could be taken for the generation of lead molecules for the drug discovery of antimicrobial and antioxidant entities from quinoline.

Cite this: *Eur. J. Chem.* **2021**, *12(1)*, 37-44 **Journal website**: www.eurjchem.com

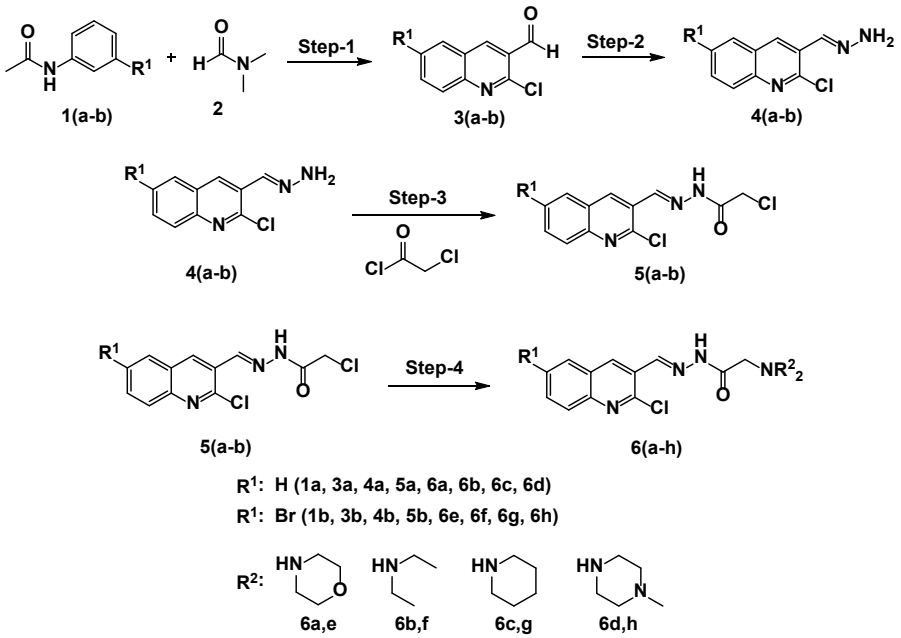
1. Introduction

The reports from the World Health Organization (WHO) indicate that public health has a major concern due to population explosion and an increase in widespread epidemic diseases. Genomic studies on various microorganisms have shown that prolonged use of antibiotics makes these microorganisms more resistant against them [1]. The literature investigation reveals that a number of quinoline derivatives possess antileishmanial [2], cytotoxicity [3,4], antibacterial, anti-tuberculosis [5], antimalarial [6,7], anti-inflammatory [8] and HIV-1 integrase activities [9]. Quinoline derivatives have been developed for the treatment of many diseases like malaria [10], HIV [11], tumor [12], and antibacterial infections [13].

The hydrazide analogs with azomethine (-CONHN=CH-) functionality were found to exhibit prominent pharmacological and biological activities [14,15] and antagonistic to inflamematory [16]. The *in vitro* metabolic studies suggested that the hydrazide hydrazone functionality can easily undergo hydrolytic reactions, which is a benefit to treat various life-threatening diseases [17,18]. Hydrazide hydrazone's are the most essential intermediates to build various heterocyclic rings utilizing the hydrogen segment of -CONHN=CH azomethine group [19]. The fast-growing microbial immunity to conventional anti-infectious agents has necessitated the continuing search for new classes of compounds with novel methods of antimicrobial activity [20-22]. The study depicts that the compound 2-(7-fluoro-2-methoxyquinolin-8-yl)acetohydrazide hydrazone derivatives exhibit good antibacterial activity [23]. Eswaran *et. al*. have reported the synthesis and investigation of antibacterial properties of 1-(2,8-*bis*(trifluoromethyl)quinolin-4-yl)-4-methylsemicarbazide derivatives which showed promising antibacterial activity [24].

The substance 2-chloroquinoline-3-carbaldehyde was prepared by the Vilsmeier-Haack formylation method, the advanced part of this 2-chloro-3-[hydrazinylidenemethyl] quinoline was obtained by treating hydrazine hydrate [25]. In view of the above literature study, the hydrazide hydrazones were found to be having more potential to exhibit good biological activity. Hence, an attempt is made in designing molecules by retaining the pharmacophore hydrazide hydra-

https://dx.doi.org/10.5155/eurjchem.12.1.37-44.2038



Scheme 1. Synthesis of compounds **6a-h**.

zone functionality at the 3rd position of the quinoline to exhibit maximum biological response. The idea behind the research is to generate molecules with profound biological activities against infectious organisms along with their antioxidant potential.

2. Experimental

2.1. Materials and methods

The reagents and chemicals were obtained from Hi-Media, India, Sigma-Aldrich, India and SD-Fine chemical, India. The monitoring of reactions on precoated silica gel aluminum TLC plates (Merck). An open capillary method was adopted to check the melting point using the raga melting point apparatus. The synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The IR spectra were recorded in KBr on a Perkin-Elmer model 1620 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Spectrospin DPX400 (400 MHz) spectrometer in $CDCl_3$ solvent. The following abbreviations were used to designate the peak multiplicity s-singlet, d-doublet and t-triplet and m-multiplet and the values are expressed in δ (ppm). The mass spectrum has been recorded on FAB mass spectrometer (JEOL SX 102/DA-6,000).

2.2. Synthesis

2.2.1. Synthesis of compounds 3a and 3b

2.2.1.1. Synthesis of 2-chloroquinoline-3-carbaldehyde (3a)

Dimethylformamide (22.2 mmol) was taken in a 100 mL round bottom flask. To this, phosphorus oxychloride (44.4 mmol) was added dropwise maintaining a temperature of 0-5 °C, and allowed the reaction to attain room temperature with constant stirring. Acetanilide (7.4 mmol) was added to the reaction mixture and the stirring was continued at 55-60 °C for 8 h on an oil bath. After completion of the reaction, the mixture was poured into ice-cold water; the precipitate thus formed was filtered under suction and dried [25] (Scheme 1).

2.2.1.2. Synthesis of 6-bromo-2-chloroquinoline-3-carbaldehyde (3b)

Dimethylformamide (22.2 mmol) was taken in a 100 mL round bottom flask. To this, phosphorus oxychloride (44.4 mmol) was added dropwise maintaining a temperature of 0-5 °C, and allowed the reaction to attain room temperature with constant stirring. *N*-(3-bromophenyl)acetamide (7.4 mmol) was added to the reaction mixture and the stirring was continued at 55-60 °C for 8 h on an oil bath. After completion of the reaction, the mixture was poured into ice-cold water; the precipitate thus formed was filtered under suction and dried [25] (Scheme 1).

2.2.2. Synthesis of compounds 4a and 4b

2.2.2.1. Synthesis of 2-chloro-3-(hydrazonomethyl) quinoline (4a)

The compound 2-chloroquinoline-3-carbaldehyde (**3a**) (4.8 mmol) was taken in a round bottom flask (100 mL), to this, methanol (10 mL) was added and cooled to 0-5 °C by keeping in an ice bath followed by the addition of hydrazine hydrate (19.4 mmol) dropwise. The reaction mixture is allowed to warm to room temperature with constant stirring and is stirred an additional 2-3 h with occasionally monitoring by TLC. After completion of the reaction, the solid formed was filtered under suction and dried [25,26] (Scheme 1).

2.2.2.2. Synthesis of 6-bromo-2-chloro-3-(hydrazonomethyl) quinoline(4b)

The compound 6-bromo-2-chloroquinoline-3-carbaldehyde (**3b**) (4.8 mmol) was taken in a round bottom flask (100 mL), to this methanol (10v) was added and cooled to 0-5°C by keeping in an ice bath followed by the addition of hydrazine hydrate (19.4 mmol) dropwise. The reaction mixture is allowed to warm to room temperature with constant stirring and is stirred an additional 2-3 h with occasionally monitoring by TLC. After completion of the reaction, the solid formed was filtered under suction and dried [25,26] (Scheme 1).

2.2.3. Synthesis of compounds 5a and 5b

2.2.3.1. Synthesis of 2-chloro-N'-((2-chloroquinolin-3-yl) methylene)acetohydrazide (5a)

The compound 2-chloro-3-(hydrazonomethyl)quinoline (**4a**) (4.8 mmol) was taken in a 50 mL round bottom flask. To this, DCM (10 mL) and 2-chloroacetyl chloride (7.2 mmol) was added dropwise maintaining a temperature of 0-5 °C. The reaction mixture was stirred at ambient temperature for 2-3 h on a magnetic stirrer with occasionally monitored by the TLC. After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ solution, extracted with DCM, and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get a solid product [25,27,28] (Scheme 1).

2.2.3.2. Synthesis of N'-((6-bromo-2-chloroquinolin-3-yl) methylene)-2-chloroacetohydrazide (5b)

The compound 6-bromo-2-chloro-3-(hydrazonomethyl) quinoline (**4b**) (4.8 mmol) was taken in a 50 mL round bottom flask. To this, DCM (10 mL) and 2-chloroacetyl chloride (7.2 mmol) was added dropwise maintaining a temperature of 0-5 °C. The reaction mixture was stirred at ambient temperature for 2-3 h. on a magnetic stirrer with occasionally monitored by the TLC. After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ solution, extracted with DCM, and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get solid [25,27,28] (Scheme 1).

2.2.4. Synthesis of compounds 6a-d

2-Chloro-*N*'-((2-chloroquinolin-3-yl)methylene) acetohydrazide (**5a**) (3.5 mmol)and DMF (20 mL) was taken in a 50 mL round bottom flask. To this, dry K_2CO_3 (7.0 mmol) was added followed by secondary amines (Morpholine, diethylamine, piperidine and 1-methylpiperazine) at 0-5 °C. The reaction was stirred at 25-30 °C for 3-4 h on a magnetic stirrer with occasionally monitoring by TLC. After completion of the reaction, the reaction mixture was quenched with cold water and extracted with ethyl acetate, dried over Na_2SO_4, and filtered. The organic layer was concentrated under reduced pressure and controlled temperature to get a solid product (68-70%) (Scheme 1).

*N'-((2-Chloroquinolin-3-yl) methylene)-2-morpholinoaceto hydrazide (**6a**)*: Color: Light brown. Yield: 68%. M.p.: 156-159 °C. FT-IR (KBr, ν, cm^{-1}): 3459 (N-H), 2933 (C-H), 1694 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$,δ, ppm): 10.39 (s, 1H, NH), 8.97 (s, 1H, CH=N), 8.60 (s, 1H, Ar-H), 8.019-7.997 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.918-7.898 (d, *J* = 7.6Hz, 1H, Ar-H), 7.762-7.749 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.603-7.588 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.573-3.561 (t, *J* = 2 Hz, 4H, CH_2OCH_2), 3.10 (s, 2H, CH_2C=O), 2.486-2.482 (t, *J* = 2 Hz, 4H, CH_2NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.6, 158.9, 148.0, 143.1, 136.7, 131.7, 128.5, 128.3, 127.7, 127.0, 125.2 (Ar-C), 66.0 (COC), 60.9 (CC=O), 53.6 (CNC). MS (EI, *m/z* (%)): 333.6 (M+1).

*N'-((2-Chloroquinolin-3-yl) methylene)-2-(diethylamino)ace tohydrazide (**6b**)*: Color: Brown. Yield: 78%. M.p.: 164-167 °C. FT-IR (KBr, ν, cm^{-1}): 3428 (N-H), 2930 (C-H), 1696 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.47 (s, 1H, NH), 8.99 (s, 1H, CH=N), 8.60 (s, 1H, Ar-H), 8.019-7.997 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.918-7.898 (d, *J* = 7.6Hz, 1H, Ar-H), 7.784-7.770 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.583-7.568 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.19 (s,2H, CH_2C=O), 2.574-2.542 (q, *J*= 4.8 Hz, 4H, CH_2NCH_2), 1.131-1.111 (t, *J*= 7.2 Hz, 6H, CH_3,CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.6, 158.9, 148.0, 143.1, 136.7, 131.7, 128.5, 128.3, 127.7, 127.0, 125.2, 61.9 (CC=O), 47.0 (CNC), 11.7 (CH_3). MS (EI, *m/z* (%)): 319.7 (M+1).

*N'-((2-Chloroquinolin-3-yl) methylene)-2-(piperidin-1-yl)ace tohydrazide (**6c**)*: Color: Pale white. Yield: 75%. M.p.: 178-180 °C. FT-IR (KBr, ν, cm^{-1}): 3553 (N-H), 2993 (C-H), 1693 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.47 (s, 1H, NH), 8.99 (s, 1H, CH=N), 8.60 (s, 1H, Ar-H), 8.019-7.997 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.918-7.898 (d, *J* = 7.6Hz, 1H, Ar-H), 7.784-7.770 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.603-7.588 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.19 (s,2H, CH_2C=O), 2.57-2.54 (t, *J* = 4.8 Hz, 4H, CH_2NCH_2), 1.70-1.61 (m, 4H, CH_2,CH_2), 1.538-1.522 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 167.4, 149.0, 148.1, 143.0, 136.8, 131.7, 128.6, 128.4, 127.8, 127.1, 125.4 (Ar-C), 61.9 (CC=O), 55.2 (CNC), 26.2 (CH_2), 23.6 (CH_2). MS (EI, *m/z* (%)): 331.8 (M+1).

*N'-((2-Chloroquinolin-3-yl) methylene)-2-(4-methylpipera zin-1-yl)acetohydrazide (**6d**)*: Color: Light brown. Yield: 74%. M.p.: 195-197 °C. FT-IR (KBr, ν, cm^{-1}): 3459 (N-H), 2933 (C-H), 1694 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.34 (s, 1H, NH), 8.98 (s, 1H, CH=N), 8.62 (s, 1H, Ar-H), 8.076-8.055 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.998-7.967 (d, *J* = 8 Hz, 1H, Ar-H), 7.788-7.774 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.589-7.571 (t, *J* = 7.6 Hz, 1H, Ar-H), 3.25 (s, 2H, CH_2C=O), 2.67-2.54 (m, 8H, CH_2NCH_2), 2.31 (s, 3H, CH_3-N). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.6, 158.9, 148.0, 143.1, 136.79, 131.7, 128.5, 128.3, 127.7, 127.0, 125.2 (Ar-C), 60.9 (CC=O), 55.0 (CNC), 53.6 (CNC), 45.9 (C-N). MS (EI, *m/z* (%)): 346.6 (M+1).

2.2.5. Synthesis of compounds 6e-f

N'-((6-Bromo-2-chloroquinolin-3-yl) methylene)-2-chloro acetohydrazide (**5b**) (3.5 mmol) and DMF (20 mL) was taken in a 50 mL round bottom flask. To this, dry K_2CO_3 (7.0 mmol) was added followed by secondary amines (Morpholine, diethyl amine, piperidine and 1-methylpiperazine) at 0-5 °C. The reaction was stirred at 25-30 °C for 3-4 h on a magnetic stirrer with occasionally monitoring by TLC. After completion of the reaction, the reaction mixture was quenched with cold water and extracted with ethyl acetate, dried over Na_2SO_4, and filtered. The organic layer was concentrated under reduced pressure and controlled temperature to get a solid product (68-70%) (Scheme 1).

*N'-((6-Bromo-2-chloroquinolin-3-yl) methylene)-2-morpholi noacetohydrazide (**6e**)*: Color: Pale brown. Yield: 68%. M.p.: 147-149 °C. FT-IR (KBr, ν, cm^{-1}): 3487 (N-H), 2928 (C-H), 1699 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.39 (s, 1H, NH), 8.97 (s, 1H, CH=N), 8.51 (s, 1H, Ar-H), 8.019-7.997 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.918-7.898 (d, *J* = 7.6Hz, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 3.10 (s,2H, CH_2C=O), 3.584-3.573 (t, *J*= 7.2 Hz, 4H, CH_2OCH_2), 2.486-2.482 (t, *J*= 1.6 Hz, 4H, CH_2NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.7, 158.9, 148.1, 143.1, 136.8, 131.7, 128.6, 128.3, 127.7, 127.1, 125.3 (Ar-C), 66.0 (COC), 60.9 (CC=O), 53.6 (CNC). MS (EI, *m/z* (%)): 412.4 (M+1).

*N'-((6-Bromo-2-chloroquinolin-3-yl) methylene)-2-(diethyl amino)acetohydrazide (**6f**)*: Color: Light brown. Yield: 58%. M.p.: 197-199 °C. FT-IR (KBr, ν, cm^{-1}): 3490 (N-H), 2924 (C-H), 1699 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.47 (s, 1H, NH), 8.99 (s, 1H, CH=N), 8.60 (s, 1H, Ar-H), 8.019-7.997 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.766-7.762 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.60-7.56 (m, 1H, Ar-H), 3.19 (s,2H, CH_2C=O), 2.574-2.562 (q, *J*= 2.0 Hz, 4H, CH_2NCH_2), 1.707-1.698 (t, *J*= 3.6 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.6, 159.0, 148.0, 143.1, 136.7, 131.7, 128.5, 128.3, 127.7, 127.0, 125.2 (Ar-c), 60.9 (CC=O), 46.0 (CNC), 11.7 (CH_3). MS (EI, *m/z* (%)): 398.5 (M+1).

*N'-((6-Bromo-2-chloroquinolin-3-yl) methylene)-2-(piperi din-1-yl)acetohydrazide (**6g**)*: Color: Light brown. Yield: 65%. M.p.: 215-218 °C. FT-IR (KBr, ν, cm^{-1}): 3488 (N-H), 2924 (C-H), 1657 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.42 (s, 1H, NH), 8.96 (s, 1H, CH=N), 8.62 (s, 1H, Ar-H), 8.02-7.99 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.918-7.898 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 3.19 (s, 2H, CH_2C=O), 2.57-2.56 (t, *J* = 4.8 Hz, 4H, CH_2NCH_2), 1.70-1.61 (m, 4H, CH_2,CH_2), 1.61-1.50 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 167.1, 157.0, 148.5, 143.1, 136.7, 131.5, 128.6, 128.3, 127.9, 127.1, 125.2 (Ar-C), 61.9

(CC=O), 55.2 (CNC), 26.2 (CH_2), 23.6 (CH_2). MS (EI, *m/z* (%)): 410.6 (M+1).

*N'-((6-Bromo-2-chloroquinolin-3-yl)methylene)-2-(4-methyl piperazin-1-yl)acetohydrazide (**6h**):* Color: White. Yield: 59%. M.p.: 223-226 °C. FT-IR (KBr, ν, cm^{-1}): 3387 (N-H), 2924 (C-H), 1657 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.34 (s, 1H, NH), 9.22 (s, 1H, CH=N), 8.98 (s, 1H, Ar-H), 8.644-8.622 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.91-7.89 (t, *J* = 8 Hz, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 3.25 (s, 2H, CH_2C=O), 2.67-2.54 (m, 8H, CH_2NCH_2), 2.31 (s, 3H, CH_3N). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.5, 158.7, 148.0, 143.2, 136.71, 131.5, 128.3, 128.1, 127.9, 127.1, 125.5 (Ar-C), 60.9 (CC=O), 55.0 (CNC), 53.6 (CNC), 45.9 (CN). MS (EI, *m/z* (%)): 425.3 (M+1).

2.3. Biological activity

2.3.1. In silico ADME(T) studies

The QSAR parameters are employed to optimize the molecular descriptors. The properties help to understand physicochemical and pharmacokinetics of their potentiality for ADME (Absorption, Distribution, Metabolism, Excretion) Toxicity [29-35]. The study enables the evaluation of biologically active and inactiveness of molecules, undesirable functional groups. The *P*log BB, log HIA, Caco-2 cell permeability (PCaco), Log pGI, Log Papp, and aqueous solubility (*P*log S) help to know to understand the metabolism of active compounds [29-35]. The study also helps to envisage the toxic effect of different routes of drug administration.

2.3.2. Pharmacokinetics properties: ADMET screening in silico profile

The compound required to elicit a biological response depends upon bioavailability. Poor bioavailability leads to infectiveness. To overcome such a problem, predicting such parameters before drug development is to optimize and important to reduce the cost. Hence, molecular parameters study utilizing pharmacokinetic parameters is essential [29-32].

2.3.3. Antimicrobial activity

The *in vitro* antimicrobial screening of the synthesized compounds **6a**-**h** was carried out by using a cup plate method using nutrient agar (NA) medium A, with different bacterial strains *viz. Staphylococcus aureus* (ATCC-25923), *Vibrio cholera* (ATCC-39315), *Pseudomonas aeruginosa* (ATCC-27853), and *Escherichia coli* (ATCC-25922). The antifungal activities were evaluated by using potato dextrose agar medium B (peptone 1%, distilled water 1000 mL, agar 2%, and glucose 4%) with a pH = 5.6 with different fungal strains *Aspergillus niger* (ATCC-13497), *Candida albicans* (ATCC-10231), *Penicillin chryso genum* (ATCC-10106) and *Cladosporium oxysporum* (ATTC-76499). These microorganisms obtained from Microbiology Department, Kuvempu University, Jnana Sahyadri, Shankarghatta, Shimoga, India. The test solutions were prepared with DMSO solvent and diluted with double distilled water to obtain concentrations of 1000, 500, and 250 µg/mL. The test microorganisms have been maintained in slant tubes as solid culture. The solid slant was prepared and inoculated from the original stock culture and then finally the liquid medium was inoculated from the above solid slants. The inoculated bacterial microorganisms were allowed to incubate at 37 °C for 24 h and fungal species at 28 °C for 24 h, respectively. The liquid agar media of 20 mL was taken in the McCartney bottle and that was sterilized in an autoclave for 15 min at 121 °C and 15 psi [36,37].

The sterilized media was poured into the sterilized Petri plates aseptically in a horizontal laminar airflow chamber. The layers of media were uniformly distributed and were allowed to solidify in the aseptic chamber, followed by inoculating the bacterial strains separately in the petri plates. The suspension was adjusted with sterile saline to make a concentration of approximately 1.0×10^7 CFU/mL. For the establishment of activity, the inoculated Petri plates were divided into three quarters parts and to each quarter a well was made in the media with the help of a sterilized cork borer (9 mm). The known concentrations of the standard drug amoxicillin, fluconazole, and test compounds were added to the particular labeled wells. Then, the applied plates were kept in the refrigerator for 10 min, followed by incubation at 37 °C for 24 h for bacterial species and 28 °C for 72 h for fungal species, respectively [36-40].

2.3.4. Antioxidant activity

2,2'-Diphenyl-1-picrylhydrazyl (DPPH) is a stable free radical, it can accept an electron or hydrogen radical to become a steady diamagnetic molecule. Due to its odd number of electrons, the methanol solution of DPPH shows a strong absorption band at 517 nm. DPPH free radical reacts with assorted electron donating molecules (reducing agents or antioxidants), when electrons become paired off, it leads to bleaching of the DPPH solution. This consequences in the formation of the colorless 2,2'-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be projected quantitatively by measuring the decrease in absorbance at 517 nm.

Equal volume of 100 µM 2,2'-diphenyl-1-picrylhydrazyl (DPPH) in methanol was added to different concentrations of test compounds (100 µM/mL) in methanol, assorted well and kept in the dark for 20 min. The absorbance at 517 nm was measured by using the spectrophotometer UV-1650, Shimadzu [41-43]. By plotting the percentage of DPPH· scavenging against concentration, it gives the standard curve. The percentage of scavenging was calculated according to Equation (1).

$$\%\ \text{Inhibition} = \frac{\text{Absorbance of blank - Absorbance of test}}{\text{Absorbance of blank}} \times 100 \quad (1)$$

3. Results and discussion

3.1. Chemistry

The 2-chloroquinoline-3-carbaldehyde (**3a**) was synthesized by Vilsmeier Haack reaction [44]. Upon reacting acetanilide (**1**) with dimethyl formamide (**2**) in the presence of phosphorousoxy chloride at 50 °C for 8 h. The obtained quinoline aldehyde **3a** was further reacted with hydrazine hydrate in the presence of methanol to yield 2-chloro-3-(hydrazonomethyl)quinoline (**4a**). The 2-chloro-3-(hydrazono methyl)quinoline (**4a**) was reacted with 2-chloroacetyl chloride to yield 2-chloro-*N'*-((2-chloroquinolin-3-yl)methylene)aceto hydrazide (**5a**) which upon reaction with secondary amines (Morpholine, diethylamine, piperidine and 1-methylpipera zine) yield the target compounds **6a**-**d** (Scheme 1). The purification of the compounds **6a**-**h** was achieved by column chromatography using *n*-hexane: ethyl acetate gradient as the mobile phase. The structures of the compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. Similar experimental methods were applied for 6-bromo-2-chloro quinoline-3-carbaldehyde (**3b**) and we obtained the compounds **6e**-**h**.

The ^{1}H NMR spectrum of the prepared compounds revealed a singlet signal corresponding to the methylene protons at δ 3.25-3.10 ppm. CH=N singlet signal resonates at δ 9.22-8.96 ppm and singlet signal corresponds to NH proton at δ 10.47-10.34 ppm. The ^{13}C NMR spectrum of the synthesized compounds revealed a signal corresponds to methylene carbon at δ 61.9-60.9 ppm.

Table 1. ADME and pharmacological parameters prediction for the compounds**6a-h** using ADME SAR toolbox.

Compound	*P*log BB [a]	Log HIA [b]	PCaco [c]	Log pGI (substrate) [d]	Log pGI (non-inhibitor) [e]	*P*log S [f]	Log P_{app} [g]
6a	0.8814	0.9957	0.5353	0.6850	0.6924	-2.9531	1.0229
6b	0.8242	0.9947	0.5293	0.7943	0.8627	-3.0447	0.9365
6c	0.8798	0.9795	0.5999	0.7101	0.6695	-3.2752	0.4522
6d	0.8754	0.9884	0.5465	0.8332	0.5257	-3.1011	0.5510
6e	0.9155	0.9923	0.5903	0.6474	0.5924	-3.4830	0.7029
6f	0.9074	0.9947	0.5895	0.6389	0.6521	-3.5299	0.6933
6g	0.8643	0.9920	0.5499	0.8274	0.5867	-3.1759	0.5444
6h	0.8686	0.9859	0.5981	0.7019	0.7232	-3.3413	0.4480
Amoxicillin	0.9967	0.9008	0.8722	0.5741	0.9665	-3.0180	-0.0502
Fluconazole	0.9382	0.9894	0.8867	0.6008	0.8782	1.8626	1.3598
Ascorbic acid	0.8532	0.7710	0.6559	0.8696	0.9347	0.1081	-0.3148

[a] Predicted blood/brain barrier partition coefficient (1-high penetration, 2- medium penetration and 3- Low penetration).
[b] Predicted Human intestinal absorption in nm/s (acceptable range: 0 poor, > 1 great).
[c] Predicted Caco-2 cell permeability in nm/s (acceptable range: -1 is poor, 1 is great).
[d] Predicted P-glycoprotein substrate in nm/s (acceptable range of -5 is poor, 1 is great).
[e] Predicted P-glycoprotein inhibitor in nm/s (accepted range: 0 to 1).
[f] Predicted aqueous solubility (concerned value is 0-2 highly soluble).
[g] Predicted probability of Caco-2 cell permeability in cm/s (Concern value is -1 to 1).

Table 2. LD_{50} and probability of health effects of compounds **6a-h** using ACD/ I-Lab 2.0.

ADME-TOX parameters	Intraperitoneal [a]	Oral [a]	Intravenous [a]	Subcutaneous [a]
6a	910(0.5)	610(0.2)	57(0.31)	210(0.11)
6b	940(0.5)	630(0.2)	52(0.49)	220(0.16)
6c	930(0.5)	490(0.3)	61(0.41)	190(0.28)
6d	920(0.5)	480(0.3)	58(0.30)	250(0.12)
6e	1220(0.2)	510(0.3)	50(0.39)	160(0.20)
6f	1140(0.4)	470(0.3)	51(0.47)	200(0.19)
6g	1100(0.5)	490(0.2)	58(0.40)	180(0.28)
6h	1220(0.3)	480(0.3)	62(0.41)	240(0.11)
Amoxicillin	310 (0.8)	880(0.5)	110 (0.67)	400(0.52)
Fluconazole	1200(0.7)	1000(0.5)	580(0.47)	2700(0.23)
Ascorbic acid	1100(0.7)	4500(0.6)	820(0.58)	2700(0.50)

[a] Estimated LD_{50}-mouse value in mg/kg after intraperitoneal, oral, intravenous, and subcutaneous administration.

The FTIR spectrum of prepared compounds revealed a peak corresponds to N-H at 3387-3553 cm^{-1}, C-H signal resonates at 2924-2993 cm^{-1} and the signal corresponds to C=O at 1657-1699 cm^{-1}.

3.2. ADME Prediction

The *in silico* predicted pharmacokinetic (ADME) properties of all prepared compounds include blood/brain partition coefficient (*P*log BB), human intestinal absorption (log HIA), Caco-2 cell permeability (PCaco), P glycoprotein substrate and noninhibitor (log pGI), aqueous solubility (*P*log S), probability of Caco-2 cell permeability (log P_{app}) and are given in Table 1. The transport of drug metabolites is permeable if log HIA (Human intestinal absorption) and PCaco-2 (cell permeability) are in the positive range. Maximum absorption of compounds enhances the maximum response to protein. The functional groups of compounds such as Br, Cl, F, or methoxy had high partition co-efficient values [45]. This leads to the accumulation of compounds in the human intestine and less involved in metabolism. The human intestinal range of absorption was between -5 to +1, considered within the acceptable range for compounds **6a**-**h**. The solubility of compounds **6a**-**h** in aqua lies in the range of 0 (poor) to 2 (good). The log P_{app} stated that the compounds had good permeability on lipid absorption and metabolism. While the reference compound and compounds **6a**-**h** were within the acceptable range (Table 1). The overall results predicted that the tested compounds have good drug-like, lead-like, and fragment-like properties.

3.3. Toxicity-LD_{50} prediction

The toxicities of the compounds **6a**-**h** were analyzed upon lethal dosages on different organs. The LD_{50} and health effects were also predicted using software (ACD/I-Lab 2.0). LD_{50} of the hits notice the increasing potential of acute toxicity when administered through oral, intraperitoneal, intravenous, and subcutaneous on mouse models. The comparative study of reference compounds with tested compounds on oral, subcutaneous, intraperitoneal, and intravenous is low. The results suggest that no contradictions for compounds **6a**-**h** were observed with the tested dosages. The possibility of a negative effect of compounds **6a**-**h** has found to be less on various organs (Table 2).

3.4. Antibacterial activity

The antibacterial studies were conducted against viz. *P. aeruginosa*, *S. aureus*, *V. cholera*, and *E. coli* with standard Amoxicillin. The compounds **6a**, **6c**, **6e**, and **6g** showed promising activity profile against *P. aeruginosa* with a zone of inhibition of 28±0.2, 26±0.1, 27±0.2 and 25±0.2, respectively, at 1000 µg/mL. The compounds **6a**, **6f**, and **6h** have shown promising activity against *E. coli* with zone of inhibition of 29±0.2, 28±0.3 and 27±0.3, respectively, at 1000 µg/mL. The compounds **6a**-**h** have exhibited moderate activity against *S. aureus* and *V. cholera* (Table 3).

3.5. Antifungal activity

The antifungal studies were conducted against fungal species *C. oxysporum*, *P. chrysogenum*, *C. albicans*, and *A. niger*, along with standard fluconazole. The compounds **6b**,**6c**, and **6e** showed a promising activity profile on *C. oxysporum* with zone of inhibition of 21±0.4, 22±0.2 and 21±0.2, respectively, with 1000 µg/mL. The compounds **6c**, **6e**, **6f**, **6g**, and **6h**showed promising activity against *P. chrysogenum* with zone of inhibition of 25±0.20, 22±0.2, 24±0.2, 23±0.2 and 22±0.2, respectively, at 1000 µg/mL. The synthesized target molecules 6a-h have exhibited moderate activity against *C. albicans* and *A. niger* (Table 4).

3.6. Structure activity relation

The structure activity relation (SAR) study revealed that the activity is mainly due to substitution on quinoline ring, the

Table 3. The *in vitro* antibacterial potential of compounds **6a-h**.

Compound	Conc. of test sample (µg/mL)	Zone of inhibition in mm (mean±SD) n=3			
		P. aeruginosa	*S. aureus*	*V. cholera*	*E. coli*
6a	1000	28±0.2	21±0.1	18±0.1	29±0.2
	500	26±0.1	17±0.3	15±0.1	22±0.1
	250	21±0.1	11±0.1	11±0.1	14±0.2
6b	1000	21±0.2	16±0.1	17±0.2	18±0.1
	500	18±0.1	13±0.1	13±0.1	16±0.2
	250	14±0.1	9±0.2	12±0.1	12±0.1
6c	1000	26±0.1	22±0.2	21±0.2	22±0.2
	500	21±0.2	17±0.1	18±0.1	17±0.2
	250	18±0.1	15±0.2	14±0.2	13±0.1
6d	1000	19±0.3	23±0.1	17±0.2	19±0.2
	500	17±0.2	17±0.2	14±0.1	16±0.3
	250	14±0.2	13±0.2	11±0.1	11±0.1
6e	1000	27±0.2	22±0.1	19±0.1	23±0.3
	500	21±0.3	19±0.3	16±0.3	19±0.2
	250	19±0.1	13±0.2	9±0.2	12±0.2
6f	1000	19±0.2	21±0.1	17±0.1	28±0.3
	500	16±0.3	19±0.3	15±0.3	21±0.1
	250	11±0.1	12±0.2	11±0.2	19±0.2
6g	1000	25±0.2	19±0.1	19±0.1	19±0.3
	500	21±0.3	16±0.3	15±0.3	18±0.2
	250	19±0.1	13±0.2	13±0.2	11±0.1
6h	1000	21±0.2	19±0.1	19±0.1	27±0.3
	500	18±0.3	17±0.3	17±0.1	21±0.2
	250	15±0.1	13±0.2	12±0.2	19±0.2
Standard (Amoxicillin)	1 mg/mL	32±0.2	26±0.2	28±0.1	34±0.2

Table 4. The *in vitro* antifungal potential of compounds **6a-h**.

Compound	Conc. of the test sample (µg/mL)	Zone of inhibition in mm (mean±SD) n=3			
		C. oxysporum	*P. chrysogenum*	*C. albicans*	*A. niger*
6a	1000	18±0.2	8±0.3	16±0.3	-
	500	11±0.3	-	10±0.2	-
	250	-	-	-	-
6b	1000	21±0.4	11±0.3	17±0.3	14±0.4
	500	09±0.3	-	12±0.3	09±0.3
	250	-	-	07±0.2	-
6c	1000	22±0.2	25±0.2	19±0.2	15±0.3
	500	18±0.3	21±0.3	11±0.2	-
	250	16±0.3	17±0.4	-	-
6d	1000	14±0.2	11±0.3	13±0.4	16±0.4
	500	10±0.3	-	09±0.5	11±0.3
	250	9±0.2	-	-	-
6e	1000	21±0.2	22±0.2	17±0.4	17±0.4
	500	17±0.2	9±0.2	11±0.3	11±0.3
	250	10±0.2	-	10±0.3	-
6f	1000	19±0.2	24±0.2	17±0.4	11±0.4
	500	16±0.2	16±0.2	12±0.3	-
	250	10±0.2	09±0.4	-	-
6g	1000	21±0.2	23±0.2	14±0.4	-
	500	17±0.2	9±0.2	11±0.3	-
	250	-	-	-	-
6h	1000	19±0.2	22±0.2	19±0.4	-
	500	17±0.2	9±0.2	15±0.3	-
	250	10±0.2	-	10±0.3	-
Standard (Fluconazole)	1 mg/mL	28±0.3	32±0.2	24±0.2	20±0.4

Table 5. Antioxidant activity of compounds **6a-h**.

Compound	% Inhibition (mean±SD)		
	50 µM	75 µM	100 µM
6a	20±0.25	35±0.26	41±0.26
6b	18±0.14	31±0.15	35±0.14
6c	15±0.32	28±0.31	36±0.34
6d	14±0.21	26±0.22	31±0.23
6e	19±0.30	32±0.28	40±0.29
6f	16±0.27	24±0.29	30±0.29
6g	17±0.37	25±0.36	34±0.35
6h	15±0.31	27±0.32	32±0.32
Ascorbic acid	72±0.33	84±0.35	98±0.34

* SD: Standard deviation.

compounds having Cl substitution at 2nd position, and imine bond substitution present at the 3rd position of quinoline. The hydrazide analogs with azomethine (-CONHN=CH-) functionnality are found to establish prominent pharmacological and biological activities. The hydrazide hydrazone functionalities can easily endure hydrolytic reactions, which is an advantage to increase the activity [17,45]. The compounds **6a**, **6c**, **6e**, and **6g** having morpholine, piperidine rings, respectively, as side chain substitution at 3rd position, exhibited promising activity. The substitution of a metabolically stable heterocyclic ring (pyrrolidine and morpholine) in the short chain analogs leads to an increase in activity [18]. The basic nature of the side chain is essential for the accumulation of the drug within the acidic food vacuole of the parasite [46].

3.7. Antioxidant activity

The antioxidant properties of the novel synthesized compounds **6a**-**h** were found that the DPPH· method gave good antioxidant profile for the synthesized compounds. The antioxidant properties of the compounds exhibited by both electron withdrawing (Cl, Br) groups and electron donating (methoxy, methyl) functionalities. The *in vitro* antioxidant evaluation of the synthesized compounds revealed that among these compounds **6a**, **6b**, **6c**, and **6e** exhibited the maximum antioxidant potential and the rest of them were moderate to poor (Table 5).

4. Conclusion

A series of quinoline derivatives (**6a**-**h**) were synthesized and screened for *in vitro* antimicrobial activity. The *in silico* ADMET studies of the prepared molecules were analyzed and found to be obeying the ADME properties and they were nontoxic. The compounds **6a**, **6c**, **6e**, and **6g** showed promising activity profiles against *P. aeruginosa.* The compounds **6a**, **6f** and **6h** were shown promising activity against *E. coli.* The antioxidant evaluation of the synthesized compounds revealed that among these compounds, compounds **6a**, **6b**, **6c** and **6e** were shown antioxidant potency and the rest of them were moderate to poor. The overall data represent that the molecules are found to be active but not near to the results of that of the standard. Hence, they can be taken as possible hits. Upon which, further modification can reveal compounds with good activity which may be taken up for further development.

Acknowledgments

The authors are grateful to the authorities of Kuvempu University for providing the necessary facilities to carry out the present work. The author thanks The Indian Institute of Science, Bangalore, for their kind of support in providing spectral analysis.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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