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Synthesis and biological evaluation of quinoline-quinazolinones for antimicrobial and antileishmanial potential

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In an attempt to find a new class of antimicrobial and antileishmanial agents, a series of twenty-three quinoline-quinazolinones were prepared via reaction of 8-hydroxy/methoxyquinoline-2-carbaldehyde with various substituted aminobenzamides. These compounds were screened for their antimicrobial activity against Gram-positive bacteria (*B. subtilis*), Gram-negative bacteria (*E. coli* and *P. putida*) and fungus (*C. viswanathii*) and antileishmanial activity against promastigotes of *L. donovani*. Compound **28k** exhibited highest activity against *B. subtilis* with an IC_{50} of 0.17±0.07 μM while compound **28j** exhibited highest activity against promastigotes of *L. donovani* with an IC_{50} of 6±0.0 μM.

Keywords: Antileishmanial activity, antimicrobial activity, quinoline, quinazolinone.

Introduction

Quinoline is a versatile bicyclic heterocyclic scaffold and an important pharmacophore in medicinal chemistry[1]. A quinolinic core is a structural feature of bioactive compounds exhibiting an array of biological activities like anticancer[2], anti-HIV[3], antimycobacterial[4], trypanocidal[5], anticonvulsant[6] and anti-inflammatory[7] etc. Various derivatives of quinoline with different substituents have been shown to possess antileishmanial activity, some of them (**1-6**) are shown in Fig. 1[8–12]. Quinoline derivatives have also been reported for their antibacterial and antifungal activity[13,14]. Extensive pharmacological and biochemical studies have revealed that quinolines are effective against various microbial strains (Fig. 1)[15–17]. Quinazolinone pharamacophore has also garnered the attention of researchers because of its plethora of pharmacological activities including anticonvulsant, antiviral, anticancer, anti-inflammatory, analgesic, leishmanicidal and antimicrobial[18]. In the past decades, many studies have reported their chemotherapeutic potential in the development of antileishmanial as well as antimicrobial agents (Fig. 2)[19–23].

Experimental

The chemicals and reagents purchased from Sigma-Aldrich, Merck, SD fine chemicals, Loba Chemie, Spectrochem and Central Drug House (CDH), etc. were used without further purification unless otherwise specified. Melting points were recorded on a Veego Melting point apparatus (Mumbai, India), IR spectra were recorded on FTIR spectrometer (Perkin-Elmer, USA). The ^{1}H and ^{13}C NMR spectra (internal standard TMS) were recorded at 400 and 100 MHz, respectively, on Bruker Avance III spectrometers (Bruker, Germany), and spectra on Thermo LTQ-XL mass spectrometer (Thermo, USA). Percent purity was determined at the respective λ_{max} of the compounds using HPLC (details in Supplementary Information).

*General procedure for synthesis of substituted aminobenzamides (**25**):*

Amine (**24**, 1.53 mmol) was added to a solution of isatoic anhydride (**23**, 1.53 mmol) in water and stirred at 40°C for 2–

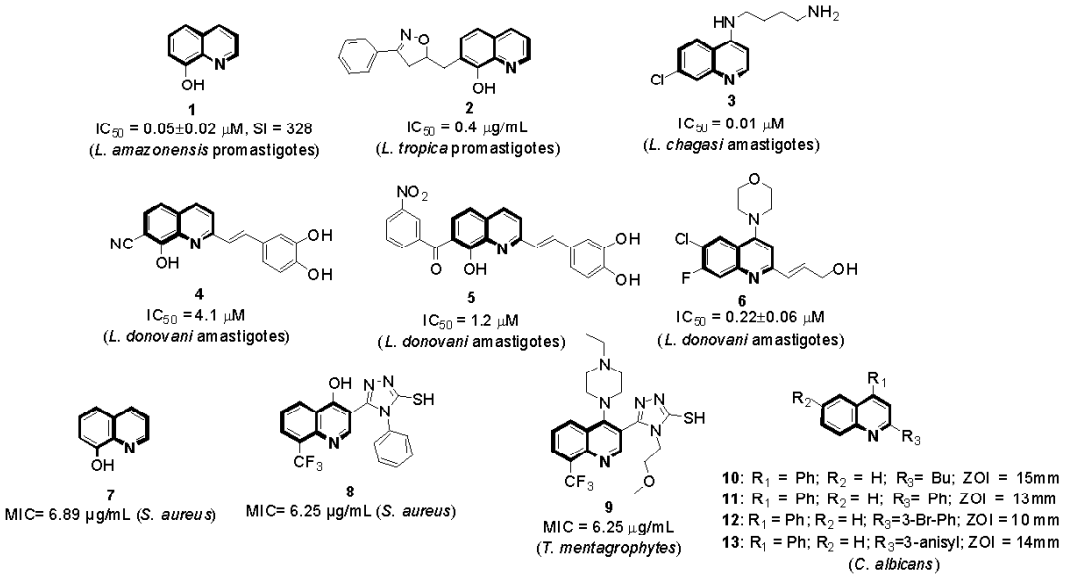


Fig 1. Quinoline derivatives as antileishmanial and antimicrobial agents.

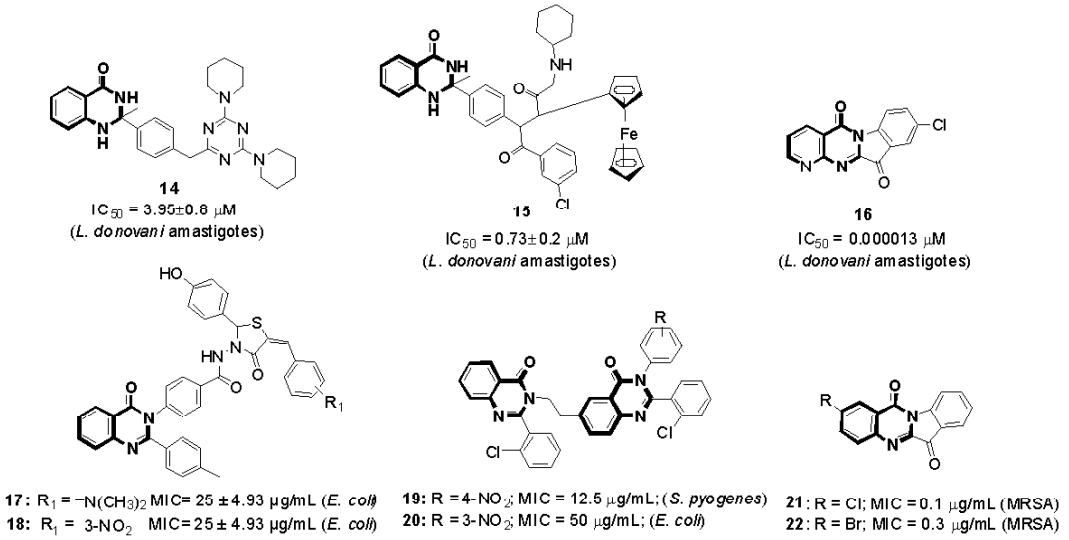


Fig. 2. Quinazolinone derivatives as antileishmanial and antimicrobial agents.

3 h. The resulting precipitates were filtered off and used for the next step without further purification[24].

*Synthesis of 8-hydroxyquinoline-2-carbaldehyde (**27**):*

SeO_2 (22.61 mmol, 1.8 eq.) was taken in 150 mL of anhydrous 1,4-dioxane and heated at 60°C. To this, 8-hydroxy-2-methylquinoline (**26**, 12.56 mmol) in 150 mL of anhydrous 1,4-dioxane was added and heated under reflux at 120°C for 2.5 h. The reaction mixture after completion was passed through celite to remove selenium. The crude product was purified by column chromatography (silica gel, 60–120 #, chloroform as eluent) to yield 8-hydroxyquinoline-2-carboxaldehyde (**27**)[25]. Yellow solid; yield 79%; m.p. 93–94°C [lit. m.p. 95–96°C].

*Synthesis of 8-methoxyquinoline-2-carbaldehyde (**32**):*

o-Anisidine **(29)** (81.2 mmol) dissolved in 6 *M* HCl (190 mL) was mixed with toluene (110 mL) by dropwise addition.

The resultant mixture was stirred for 5 min at a temperature of 100°C. Further, crotonaldehyde **(30)** (162.4 mmol, 2.0 equiv.) was added to the reaction mixture dropwise followed by heating at 120°C for 3 h. The aqueous layer was extracted with chloroform after cooling and neutralization by aqueous NaOH solution. The organic layer was dried and purified by column chromatography (silica gel 60–120 #, chloroform as eluent) to get 8-methoxy-2-methylquinoline (**31**)[26,27]. It was oxidized using SeO_2 in 1,4-dioxane using the above-mentioned procedure to obtain 8-methoxyquinoline-2-carbaldehyde (**32**).

*8-Methoxy-2-methylquinoline **(31):*** White solid; yield 67%; m.p. 122–124°C [lit. m.p. 124–125°C].

*8-Methoxyquinoline-2-carbaldehyde **(32):*** Yellow solid; yield 79%; m.p. 93–94°C [lit. m.p. 95–96°C].

*General procedure for synthesis of substituted quinazolinone-quinoline hybrids (**28a-r, 33a-e**):*

Substituted aminobenzamides **(25)** (1 equiv.) and 8-hydroxyquinoline-2 carbaldehyde **(27)** (1 equiv.) or 8-methoxyquinoline-2 carbaldehyde (**32**) (1 equiv.) were dissolved in acetonitrile. To the above solution, catalytic amount of cyanuric chloride was added and the reaction mixture was heated under reflux at 80°C for 30–120 min[28]. After the completion of reaction (TLC), the reaction mixture was purified by column chromatography on silica gel (eluent-hexane:ethyl acetate) to yield pure compound.

*2-(8-Hydroxyquinolin-2-yl)-3-isopentyl-2,3-dihydroquinazolin-4(1H)-one **(28a):*** White solid; yield 46%; m.p. 102–103°C; ESI-MS found *m/z* 384.16 $[M+Na]^+$; Anal. HPLC t_R = 4.8 min, 99.4% at 247 nm.

*3-Allyl-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28b):*** White solid; yield 32%; m.p. 95–96°C; ESI-MS found *m/z* 354.08 $[M+Na]^+$; Anal. HPLC t_R = 3.8 min, 99.9% at 244 nm.

*3-Hexyl-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28c):*** White solid; yield 34%; m.p. 108–109°C; ESI-MS found *m/z* 398.17 $[M+Na]^+$; Anal. HPLC t_R = 5.7 min, 99.8% at 245 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-pentyl-2,3-dihydroquinazolin-4(1H)-one **(28d):*** Pale yellow solid; yield 33%; m.p. 97–98°C; ESI-MS found *m/z* 384.11 $[M+Na]^+$; Anal. HPLC t_R = 4.9 min, > 99.7% at 319 nm.

*3-Butyl-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28e):*** White solid; yield 55%; m.p. 111–112°C; ESI-MS found *m/z* 370.13 $[M+Na]^+$; Anal. HPLC t_R = 4.4 min, 99.7% at 319 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-octyl-2,3-dihydroquinazolin-4(1H)-one **(28f):*** White solid; yield 30%; m.p. 156–157°C; APCI-MS found *m/z* 404.58 $[M+H]^+$; Anal. HPLC t_R = 5.7 min, 99.8% at 244 nm.

*3-(4-Chlorobenzyl)-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28g):*** White solid; yield 55%; m.p. 141–142°C; ESI-MS found *m/z* 438.01 $[M+H]^+$, 440.04 $[M+2]^+$; Anal. HPLC t_R = 5.1 min, 99.6% at 244 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-propyl-2,3-dihydroquinazolin-4(1H)-one **(28h):*** Pale yellow solid; yield 53%; m.p. 90–91°C; APCI-MS found *m/z* 334.42 $[M+H]^+$; Anal. HPLC t_R = 3.9 min, 99.4% at 260 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-isobutyl-2,3-dihydroquinazolin-4(1H)-one **(28i):*** Pale yellow solid; yield 50%; m.p. 100–101°C; APCI-MS found *m/z* 348.43 $[M+H]^+$; Anal. HPLC t_R = 4.3 min, 99.6% at 250 nm.

*3-Benzyl-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28j):*** White solid; yield 56%; m.p. 165–166°C; APCI-MS found *m/z* 382.58 $[M+H]^+$; Anal. HPLC t_R = 4.5 min, 99.6% at 320 nm.

*3-Ethyl-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28k):*** White solid; yield 62%; m.p. 89–90°C; APCI-MS found *m/z* 320.48 $[M+H]^+$; Anal. HPLC t_R = 3.6 min, 99.0% at 319 nm.

*3-Cyclopropyl-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one **(28l):*** White solid; yield 42%; m.p. 104–105°C; APCI-MS found *m/z* 332.44 $[M+H]^+$; Anal. HPLC t_R = 3.9 min, 99.2% at 319 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-(4-methylbenzyl)-2,3-dihydroquinazolin-4(1H)-one **(28m):*** White solid; yield 49%; m.p. 151–152°C; APCI-MS found *m/z* 396.49 $[M+H]^+$; Anal. HPLC t_R = 5.9 min, 98.6% at 247 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-(4-methoxybenzyl)-2,3-dihydroquinazolin-4(1H)-one **(28n):*** White solid; yield 46%; m.p. 161–161°C; ESI-MS found *m/z* 412.55 $[M+H]^+$; Anal. HPLC t_R = 4.3 min, 99.4% at 320 nm.

*2-(8-Hydroxyquinolin-2-yl)-3-(3-methoxybenzyl)-2,3-dihydroquinazolin-4(1H)-one **(28o):*** White solid; yield 50%;

m.p. 155–156°C; APCI-MS found *m/z* 412.59 $[M+H]^+$; Anal. HPLC t_R = 4.4 min, 99.4% at 320 nm.

3-(3,4-Dimethoxybenzyl)-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(28p):*** White solid; yield 56%; m.p. 168–169°C; APCI-MS found *m/z* 442.62 $[M+H]^+$; Anal. HPLC t_R = 3.9 min, 99.3% at 245 nm.

3-(3-Chlorobenzyl)-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(28q):*** White solid; yield 41%; m.p. 125–126°C; APCI-MS found *m/z* 416.64 $[M+H]^+$, 418.72 $[M+2]^+$; Anal. HPLC t_R = 5.1 min, 99.3% at 320 nm.

3-(3,4-Dichlorobenzyl)-2-(8-hydroxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(28r):*** White solid; yield 45%; m.p. 141–142°C; APCI-MS found *m/z* 450.75 $[M+H]^+$, 452.81 $[M+2]^+$; Anal. HPLC t_R = 5.9 min, 98.6% at 320 nm.

3-(4-Chlorobenzyl)-2-(8-methoxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(33a):*** White solid; yield 51%; m.p. 162–163°C; APCI-MS found *m/z* 430.72 $[M+H]^+$, 432.64 $[M+H]^+$; Anal. HPLC t_R = 4.9 min, 97.1% at 309 nm.

3-Benzyl-2-(8-methoxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(33b):*** White solid; yield 55%; m.p. 139–140°C; APCI-MS found *m/z* 396.50 $[M+H]^+$; Anal. HPLC t_R = 4.3 min, 98.6% at 309 nm.

3-(3-Chlorobenzyl)-2-(8-methoxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(33c):*** Yellow solid; yield 50%; m.p. 151–152°C; APCI-MS found *m/z* 430.62 $[M+H]^+$, 432.16 $[M+2]^+$; Anal. HPLC t_R = 4.9 min, 97.8% at 309 nm.

2-(8-Methoxyquinolin-2-yl)-3-(4-methylbenzyl)-2,3-dihydroquinazolin-4(1H)-one ***(33d):*** Yellow solid; yield 47%; m.p. 125–126°C; APCI-MS found *m/z* 410.56 $[M+H]^+$; Anal. HPLC t_R = 4.8 min, 98.2% at 308 nm.

3-Ethyl-2-(8-methoxyquinolin-2-yl)-2,3-dihydroquinazolin-4(1H)-one ***(33e):*** Yellow solid; yield 53%; m.p. 119–120°C; APCI-MS found *m/z* 334.45 $[M+H]^+$; Anal. HPLC t_R = 5.7 min, 99.7% at 320 nm.

Biological activity:

Antimicrobial activity:

The synthesized compounds were evaluated by colony counting method against *Escherichia coli* 443 and *Pseudomonas putida* 1237 (Gram-negative), *Bacillus subtilis* 1427 (Gram-positive) and fungus *Candida viswanathii* 5158 as described earlier[29,30]. All the strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh (India). The IC_{50} values were calculated by counting colonies in each plate. All the experiments were performed in triplicate.

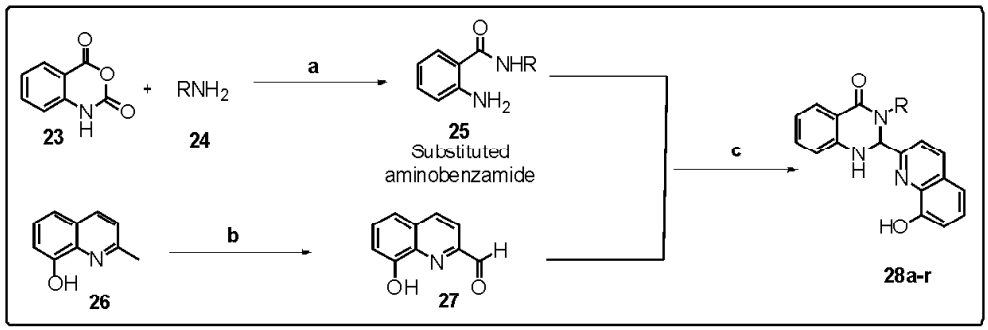
Antileishmanial activity:

Leishmania donovani promastigotes wild-type (WT, MHOM/80/IN/Dd8) were cultured as described earlier[30]. *In vitro* antileishmanial activity of *L. donovani* promastigotes was determined colorimetrically as described in the literature[30,31]. The percentage viability of promastigotes was calculated relatively by considering 100% viability in untreated promastigotes and the results were expressed as IC_{50} (half maximal inhibitory concentration). All the experiments were performed in triplicate.

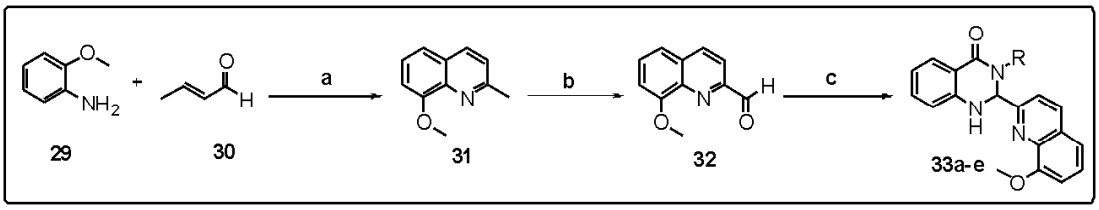
Results and discussion

Chemistry:

The detailed synthetic route employed for the synthesis of compounds (**28a-r**, **33a-e**) is outlined in Scheme 1 and Scheme 2, respectively. The synthesis was achieved by an



Scheme 1. Synthesis of 8-hydroxyquinoline-quinazolinones: (a) Water, 40°C, 2–3 h; (b) SeO_2, 1,4-dioxane, 120°C, 2.5 h; (c) Cyanuric chloride, CH_3CN, 80°C, 30–60 min.



Scheme 2. Synthesis of 8-methoxyquinoline-quinazolinone hybrids: (a) 6 *M* HCl, Toluene, 120°C, 3 h; (b) SeO_2, 1,4-dioxane, 120°C, 2.5 h; (c) Substituted aminobenzamides, cyanuric chloride, CH_3CN, 80°C, 60–120 min.

efficient and facile methodology. Various substituted aminobenzamides were synthesized by the reaction of isatoic anhydride **23** with aliphatic amines or benzyl amines **24** in water using a simpler and greener protocol as described previously in the literature[24]. After completion of reaction, the resulting precipitates were filtered off and used for the next step without any further purification. 8-Hydroxyquinoline-2-carbaldehyde was synthesized from 8-hydroxy-2-methylquinoline using selenium dioxide in anhydrous 1,4-dioxane as solvent at 120°C. This compound was purified through flash silica gel column chromatography using chloroform as eluent. 8-Methoxyquinoline-2-carbaldehyde was synthesized using modified Doebner-Miller bi-phasic method from the reaction of *o*-anisidine (**29**) and crotonaldehyde (**30**). This compound was purified through silica gel column chromatography using chloroform. Compound **31** was oxidised to 8-methoxyquinoline-2-carbaldehyde **(32)** using selenium dioxide as per the method reported earlier. The purified aldehyde (**27** or **32**) was reacted with substituted aminobenzamides using cyanuric chloride as catalyst to afford the desired compounds in moderate to good yield.

A total of twenty-three compounds were synthesized in moderate to good yields and were characterised by ^1H NMR, ^{13}C NMR, LTQ-MS and FT-IR (complete spectral data is given in Supplementary Information).

Antimicrobial activity:

The synthesized compounds were evaluated *in vitro* against bacterial strains *Escherichia coli* 443, *Pseudomonas putida* 1237, *Bacillus subtilis* 1427 and one fungus, *Candida viswanathii* 5158 using colony counting method (Table 1). The tested compounds showed better activity against Gram-positive bacteria as compared to Gram-negative bac-

Table 1. *In vitro* antimicrobial activity of quinoline-quinazolinone derivatives represented as IC_{50} (μM)

Compound	*E. coli* MTCC 443	*P. putida* MTCC 1237	*B. subtilis* MTCC 1427	*C. viswanathii* MTCC 5158
28a	NI	NI	0.37±0.04	0.85±0.02
28b	0.98±0.04	NI	0.29±0.06	NI
28c	NI	NI	0.45±0.01	NI
28d	0.96±0.08	NI	0.33±0.08	0.90±0.06
28e	NI	NI	0.25±0.04	NI
28f	NI	NI	0.58±0.05	NI
28g	0.91±0.05	NI	0.29±0.02	0.20±0.03
28h	0.26±0.02	0.49±0.08	0.22±0.08	0.32±0.01
28i	0.37±0.07	NI	0.23±0.06	0.44±0.03
28j	0.78±0.04	NI	0.78±0.02	0.66±0.01
28k	0.29±0.05	0.64±0.06	0.17±0.07	0.77±0.03
28l	NI	NI	0.89±0.02	NI
28m	NI	NI	0.39±0.04	NI
28n	0.87±0.08	NI	0.29±0.06	0.88±0.02
28o	NI	0.52±0.01	0.51±0.02	0.92±0.04

Table-1 (contd.)

28p	0.74±0.06	NI	0.19±0.05	NI
28q	NI	NI	0.36±0.07	0.24±0.06
28r	0.31±0.01	0.53±0.06	0.27±0.02	0.17±0.02
33a	NI	NI	0.55±0.01	0.78±0.06
33b	NI	0.78±0.04	NI	NI
33c	NI	NI	NI	0.96±0.05
33d	NI	NI	0.84±0.03	NI
33e	NI	NI	0.46±0.05	NI
Chloramphenicol	0.23±0.05	0.25±0.02	0.21±0.09	0.23±0.07

IC_{50}: Concentration showing 50% inhibition (μM); NI: No inhibition upto 4 μM.

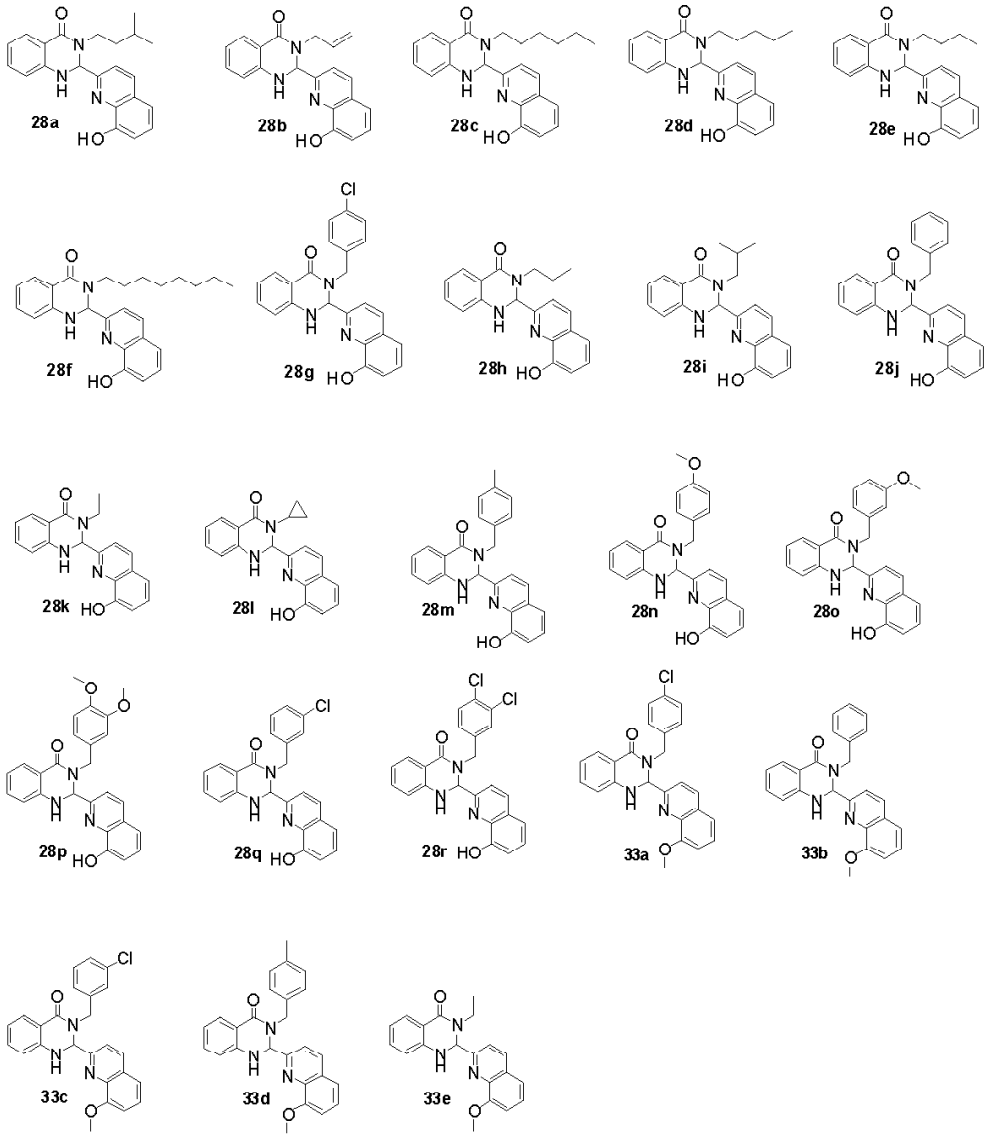


Fig. 3. Structures of synthesized derivatives.

teria. Compound **28k** showed highest activity against *B. subtilis* with IC_{50} value of 0.17±0.07 μM. Compound **28p** also exhibited better activity than chloramphenicol with IC_{50} value of 0.19±0.05 μM**.** It is suggested that increasing the length of alkyl chain has detrimental effect on activity. Compounds with 8-hydroxyquinoline moiety showed better activity than those with 8-methoxyquinoline moiety. Compound **28k** having 8-hydroxyquinoline moiety and ethyl substituent showed better activity as compared to compound **33e** having 8-methoxyquinoline moiety and ethyl substituent. Also, the compound having dimethoxy substituents (**28p**) on phenyl ring showed better activity as compared to compounds with mono methoxy substituent (**28n**, **28o**). Substitution at *para* position of the phenyl ring was favourable for activity as compared to *meta* position. Compounds **28g** and **28n** with *para* chloro and *para* methoxy substituent showed an IC_{50} of 0.29±0.02 and 0.29±0.06 μM, respectively, as compared to compound **28q** and **28o** which displayed an IC_{50} of 0.36±0.07 and 0.51±0.02 μM, respectively. Compound **28h** exhibited highest activity against *E. coli* with an IC_{50} of 0.26±0.02 μM. Compounds **28k** and **28r** displayed an IC_{50} of 0.29±0.05 and 0.31±0.01 μM, respectively. All the other tested compounds showed moderate to weak inhibition against *E. coli*. All the compounds exhibited weaker activity against *P. putida* with the highest activity displayed by compound **28h**. Compound **28h** exhibited an IC_{50} of 0.49±0.08 μM. For the fungus, *C. viswanathii* compound **28r** showed highest activity with an IC_{50} of 0.17±0.02 μM. Compounds **28g** and **28q** displayed IC_{50} value of 0.20±0.03 and 0.24±0.06 μM, respectively. The presence of dihalide substitution (**28r**) on the phenyl ring had favorable effect on activity as compared to monohalide substitution (**28g**, **28q**). The presence of halide substituent at *para* position was favorable for activity as compared to *meta* position. Compounds having alkyl substituents on the quinazolinone moiety showed moderate to weak inhibition.

Antileishmanial activity:

All the synthesized compounds were screened for *in vitro* antileishmanial activity against the promastigotes of *L. donovani*. IC_{50} values were determined using MTT assay. Miltefosine was used as positive control throughout the study. Among all the tested compounds, the following compounds were found to be active with IC_{50} values of 15±1.15 μM (**28a),** 18.5±3.53 μM (**28d**), 6±0.0 μM (**28j**) and 8±0.0 μM (**28n**), respectively, as compared to the standard drug Miltefosine with IC_{50} value of 12±0.0 μM).

Conclusions

Twenty-three quinoline-quinazolinone derivatives were synthesized and evaluated for antimicrobial and antileishmanial activity. In the antimicrobial assay, compound **28k** showed highest activity against *B. subtilis* with an IC_{50} of 0.17±0.07 μM while compound **28r** showed highest activity *C. viswanathii* with an IC_{50} of 0.17±0.02 μM. All the compounds displayed moderate to weak activity against *E. coli* and *P. putida.* In the antileishmanial assay, two compounds **28j** and **28n** exhibited better activity than the standard with an IC_{50} of 6±0.0 and 8±0.0 μM respectively.

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Supporting Information

Supporting information includes mass, IR, ^{1}H NMR and ^{13}C NMR spectral data of the synthesized compounds.

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