SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW QUINALDINE DERIVATIVES

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Abstract: A new series of quinoline derivatives incorporated to glycosides and biologically active heterocyclic moieties were synthesized starting with 6-bromo-4-hydroxyquinoline (6-bromo-4-hydroxy-2-methylquinoline) compound I. Some of the synthesized compounds were evaluated for their antibacterial and antifungal activities. Most of the tested compounds exhibited potential antibacterial activity against Gram-positive bacteria, the detailed synthesis, spectroscopic data, antibacterial and antifungal evaluation of the synthesized compounds are reported.

Keywords: quinaldine derivatives, selenadiazole, imidazole, glycosides, antibacterial, antifungal

The number of life threatening infectious diseases and microbial multidrug-resistance are responsible for great number of deaths all over the world. Drug discovery programs have reported that many natural and synthetic products are classified as antimicrobial agents. Quinoline derivatives which present in several natural products (Cinchona alkaloids) produce diverse biological and pharmacological activities such as; antimalarial (1-3), anticancer (4-6), antituberculosis (7, 8), anti-inflammatory (9, 10) analgesic (11), HIV-1 integrase inhibitors (12), antioxidant (13), anti-depressant (14), and anti-convulsant (15). Till date, this class plays an essential role in the field of antibiotic chemotherapy used for the treatment of a large number of serious bacterial infections (16-18). Many hypotheses have been advanced to account quinoline’s mode of actions (19-21). These have included DNA binding by intercalation quinoline drug with the microbial DNA thus, inhibits nucleic acid synthesis, replication and transcription (22).

The most common powerful quinoline derivatives as antibiotics are fluoroquinolones (Fig. 1). However, literature survey reported that most of them have adverse effects which may occur almost anywhere in the body. Most of fluoroquinolone drugs have fluoride atom as a central part which has the unique ability to penetrate the blood-brain barrier, entering the brain and causing undesirable effects. One of the most common adverse effects of this type of antibiotic is disturbances of the CNS (23, 24). So, the main challenge that always faces the researchers is discovering and developing new antimicrobial agents without or with the lowest adverse effects to treat serious microbial infections. Depending upon the above knowledge and in continuation to our previous efforts dealing with synthesis of various 6-bromoquinoline derivatives (25, 26) of strong antimicrobial potency, the aim of this study is to synthesize some new 6-bromoquinoline derivatives incorporated to different biologically active heterocycles that possess broad spectrum antimicrobial potency like, imidazole (27, 28), pyrazole (29, 30), furane (31, 32) or to glycosidic moieties of reported antimicrobial activity through S- or N-linkages (33, 34) to evaluate their antimicrobial
activity against a number of Gram positive, Gram negative bacteria as well as fungi. The obtained biological results have been summarized in Table 1. Examples of different marketed fluoroquinolone drugs used as broad-spectrum antimicrobials are illustrated in Fig. 1.

RESULTS AND DISCUSSION

Chemistry

The synthetic routes of the desired compounds illustrated in Schemes 1-3. Firstly, 6-bromo-4-hydroxyquinaldine, compound 1, was prepared according to the reported method (25), and was reacted with phosphorus pentasulfide in refluxing dry xylene to afford the thiol derivative 2. The latter compound 2 was coupled with a solution of the activated cyclic bromo sugar 2, 3, 3, 4, 6-tetra-O-acetyl-α-D-gluco or galacto/pyranosyl bromide at room temperature, in potassium hydroxide solution to afford the corresponding thioglycoside derivatives 3a, b. Alternatively, refluxing of compound 1 with phosphorus oxychloride afforded 6-bromo-4-chloroquinaldine 4 (25), which in turn was converted to the corresponding hydrazine derivative 5 (35) via the reaction of compound 4 with hydrazine hydrate (98%) in refluxing ethanol. Then, product 5 was reacted with the activated cyclic bromo sugar 2, 3, 4, 6-tetra-O-acetyl-α-D-gluco or galacto/pyranosyl bromide in an acidic medium to afford the corresponding N-glycoside derivatives 6a, b. Additionally, condensation of compound 5 with furfural or

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benzaldehyde in glacial acetic acid yielded the hydrazone derivatives $7a$, $b$, respectively. Furthermore, the hydrazine derivative $5$ was refluxed with methyl or phenyl isothiocyanate in dry benzene to give the corresponding thiosemicarbazide derivatives $8a$, $b$ (Scheme 1).

Also, conversion of the chloroquinaldine derivative $4$ to 4-(p-acetylanilino) derivative $9$ was proceeded according to the reported method (25). Compound $9$ was condensed with thiosemicarbazide or phenyl thiosemicarbazide to afford the thiosemicarbazone derivatives $10a$, $b$ (25) respectively. Each of the derivatives $10a$, $b$ was reacted with phenacyl bromide to afford the thiazole products $11a$, $b$. On the other hand, compounds $10a$, $b$ were reacted with ethyl bromoacetate in absolute ethanol containing few drops of piperidine to give the thiazolidinone derivatives $12a$, $b$. Moreover, compound $9$ was refluxed with sodium acetate to give the semicarbazide derivative $13$. Oxidative cyclization of compound $13$ with thionylchloride or selenium dioxide in glacial acetic acid afforded the corresponding thiadiazole or selenadiazole derivatives $14a$, $b$, respectively (Scheme 2).

Also, the hydrazino derivative $5$ was refluxed with acetyl chloride or benzoyl chloride, to give the hydrazide derivatives $15a$, $b$, respectively, which underwent cyclocondensation by refluxing in acetic acid to give the corresponding cyclized imidazooquinoline derivatives $16a$, $b$. Furthermore, compound $5$ was reacted with 2-(ethoxymethylene) malononitrile in absolute ethanol to give the pyrazolo carbonitrile derivative $17$ from which, when treated with oxalyl chloride in dry benzene, at room temperature, the pyrazolo pyrimidine derivative $18$ was obtained (Scheme 3).

The structures of the new synthesized compounds were established and confirmed on the bases of their elemental analyses and spectral data (IR, $^1$H-NMR, $^1$C-NMR and MS.)

### Biological evaluation

Some of the newly synthesized compounds were screened for their antibacterial activity using the agar dilution method (36). Ciprofloxacin and fluconazole were used as reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones of bacterial or fungal growth around the discs in mm. The minimum inhibitory concentration (MIC) measurement was determined for compounds that showed significant growth inhibition zones using the agar dilution method (36). The MIC (mg/mL) values of the active compounds against the tested bacterial and fungal strains are recorded in Table 2.

Each of $B. subtilis$ and $S. aureus$ were employed as Gram positive microorganisms, while, $E. coli$, $K. pneumonia$ and $P. aeruginosa$ were used as Gram negative bacteria. Also, $C. albicans$ represented the fungi in the present investigation. The majority of the compounds showed an antibacterial effect towards Gram positive bacteria that can be described generally as moderate effect. Tables 1, 2 depicts the antibacterial effect of the tested compounds measured as zones of inhibition as well as minimal inhibitory concentrations. The hydrazine derivative of the present nucleus (compound $7a$) is effective towards Gram positive bacteria ($S. aureus$ and $B. subtilis$), some Gram negative ($E. coli$ and $P. aeruginosa$) and $C. albicans$, a result that represents it as a promising broad spectrum antimicrobial. However, the hydrazide derivative (compound $15a$) showed antibacterial effect only toward $B. subtilis$.

The other compounds showed moderate effects against the tested Gram positive bacteria as presented in (Table 1). Also, the tested compounds showed variability in the MIC results. The results of the microbial sensitivity of the selected Gram negative microorganisms revealed that, each of the imidazo derivative $16a$ and the pyrazolo pyrimidine derivative $18$ affected $S. typhi$ with lower MIC in case of the derivative $16a$ (2 mg) about one half that of the

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**Figure 1.** Some marketed quinolone drugs
derivative 18 (4 mg). Also, *E. coli* was sensitive to compound 16a with MIC of 1 mg. On the other hand, *K. pneumoniae* and *P. aeruginosa* were moderately sensitive to compounds 6a and 7a, respectively, in almost equipotent effect. In an attempt to investigate the antifungal effect of the newly synthesized compounds, it was found that only derivative 7a showed a moderate effect against *C. albicans* (4 mg). Figure 2 summarizes the effects of the tested compounds against Gram positive microorganisms *B. subtilis* and *S. aureus*. This figure shows that the compound 7a represented the lowest MIC (0.5, 0.25 mg/mL). In general, the MIC results of the tested compounds with respect to *B. subtilis* ranged from 0.5 to 4 mg/mL, while for *S. aureus* lies between 0.25 and 4 mg/mL.

Scheme 1. Synthetic pathways of compounds 2-8a, b
**EXPERIMENTAL**

**General**

Melting points were obtained on a Barnstead 9001 Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum BX Spectrometer at cm⁻¹ scale using KBr discs. ¹H-NMR and ¹³C-NMR were recorded on a JEOL 300 MHz Spectrometer, Japan and chemical shift values were expressed in δ values (ppm) relative to tetramethylsilane (TMS) as internal standard. Coupling constants are given in Hz. The mass spectra were recorded on GCMC-QP 1000 EX Shimadzu Gas Chromatography MS spectrometer, Japan E.I.70 ev. Elemental analysis (C, H, N) were carried out at the Micro Analytical Center, Faculty of Science, Cairo University, Egypt, and were in full agreement with the proposed structures within ± 0.2-0.3% of the theoretical values. All reagents were of commercial quality and were used...
without further purification. Reaction progress was monitored by analytical thin layer chromatography (TLC) on precoated (0.75 mm) silica gel GF254 plates (E. Merck, Germany) and the products were visualized by UV light.

**Chemistry**

6-Bromo-2-methylquinoline-4-thiol (2)

To a mixture of the quinaldine derivative 1 (0.01 M) in dry xylene (10 mL), (0.02 M) of phosphorus pentasulfide was added and heated under reflux for 6 h. After cooling, the solvent was evaporated under reduced pressure the solid formed was washed well with water, filtered off, and recrystallized from DMF / water.

Yield 65%; m.p.: 235°C; IR (νmax/cm⁻¹): 1610 (C=C); ¹H-NMR (DMSO-d⁶, δ, ppm): 2.2 (s, 1H, SH), 2.3 (s, 3H, CH₃), 6.8 (s, 1H, H-3), 7.5-8.1 (m, 3H, Ar); ¹³C-NMR (DMSO-d⁶, δ, ppm): 23.9 (CH₃), 119.8, 120.6, 128.5, 129.1, 132.9, 136.4, 146.8, 158.9 (Ar-C); MS: m/z (%): 253, 255 (M⁺, M⁺2, 8.98, 8.7) consistent with the molecular formula (C₁₀H₈BrNS).

6-Bromo-2-methyl-4-(2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl thio) quinoline (3a, b)

A mixture of compound 2 (0.01 M) in ethanol (10 mL) and a solution of aqueous potassium hydroxide (0.01 M) dissolved in distilled water (5 mL) was added to a solution of 2, 3, 4, 6-tetra-O-acetyl-α-D-glucopyranosyl-β-D-galactopyranosyl bromide (0.01 M) in acetone (7 mL). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, the mixture was concentrated under reduced pressure and poured onto ice-water. The solid formed was filtered off, washed well with water and recrystallized from ethanol.

Yield 70%; m.p.: 140°C; IR (νmax/cm⁻¹): 1745 (C=O); ¹H-NMR (DMSO-d⁶, δ, ppm): 1.94-2.2 (m, 12H, 4xOAc), 2.3 (s, 3H, CH₃), 3.9 (m, 2H, 6'-H₂), 4.1-5.1 (m, 5H, H-5', 4', 3', 2', 1'), 6.8 (s, 1H, H-3), 7.5-8.1 (m, 3H, Ar); ¹³C-NMR (DMSO-d⁶, δ, ppm): 21.08 (4 x COCH₃), 23.2 (CH₃-quinaldine) 61.2 (CH₂, C-6'), 62.8, 63.9, 67.1, 70.8, 80.7 (C-5', 4', 3', 2', 1'), 119.8, 120.6, 128.5, 129.1, 132.9, 136.4, 146.8, 158.9 (Ar-C); MS: m/z (%): 583,585 (M⁺, M⁺2, 5.2, 5.0) consistent with the molecular formula (C₂₄H₂₆BrNO₉S).

6-Bromo-2-methyl-4-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl thio) quinoline (3b)

Yield 65%; m.p.: 127°C; IR (νmax/cm⁻¹): 1744 (C=O); ¹H-NMR (DMSO-d⁶, δ, ppm): 1.92-2.1 (m, 12H, 4xOAc), 2.3 (s, 3H, CH₃), 4.01 (m, 2H, 6'-H₂), 4.02-5.09 (m, 5H, H-5', 4', 3', 2', 1'), 6.85 (s, 1H, H-3)

Scheme 3. Synthetic pathways of compounds 15-18a, b
H-3), 7.5-8.1 (m, 3H, Ar); 13C-NMR (DMSO-d_6, δ, ppm): 21.08 (4 × COCH_3), 22.91 (CH_3-quinaldine), 60.91 (CH_2, C-6í), 119.8, 120.6, 128.5, 129.1, 130.2, 132.9, 143.4, 146.8, 158.9 (Ar-C and C=N); 168.3 (4 × C=O); MS: m/z (%): 583, 585 (M^+, M^2, 3.6, 2.9) consistent with the molecular formula (C_{24}H_{26}BrN_O_9).  

1-(6-Bromo-2-methylquinolin-4-yl)-2-(2',3',4',6'-tetra-O-acetyl-β-D-galacto and glucopyranosyl- yl) hydrazine (6a, b)  

To a solution of compound 5 (0.01 M) in acetone (10 mL) was added followed by addition of few drops of acetic acid, the reaction mixture was heated with stirring on a water bath at 55-65°C for 10 h. After the reaction was completed, the solvent was concentrated under reduced pressure. After cooling, the separated solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

1-(6-Bromo-2-methylquinolin-4-yl)-2-(2',3',4',6'-tetra-O-acetyl-β-D-galacto) hydrazine (6a)  

Yield 72%; m.p.: 290°C; IR (ν_{max}/cm^-1): 3380 (br, NH), 1745 (C=O), 1697 (C=C), 1553 (C=N); 1H-NMR (CDCl_3, δ, ppm): 1.97-2.02 (m, 12H, 4 x OAc), 2.31 (s, 3H, CH_3), 3.91 (s, 2H, 6í-H_2) 5.34-4.09 (m, 5H, H-5í, 4í, 3í, 2í, 1í), 6.3 (s, 1H, Ar, H-3), 7.6-8.1 (m, 3H, Ar), 9.8 (s, 1H, 1NH), 10.5 (s, 1H, NH); 13C-NMR (CDCl_3, δ, ppm): 21.85 (4 × OAc), 22.91 (CH_3-quinaldine), 60.91 (CH_3, C-6í), 61.93, 62.32, 64.34, 68.94, 71.63, (C-5í, 4í, 3í, 2í, 1í), 110.71, 111.62, 117.6, 120.6, 129.2, 144.6, 147.49, 158.5 (Ar-C and C=N); 168.3 (4 × C=O); MS: m/z (%): 281, 583 (M^+, M^2, 2.4, 2.1) consistent with the molecular formula (C_{24}H_{26}BrN_O_9).

1-(6-Bromo-2-methylquinolin-4-yl)-2-(furan-2-yl methylene) hydrazine (7a) and 1-(6-bromo-2-methylquinolin-4-yl)-2-benzylidene hydrazine (7b)  

To a solution of compound 5 (0.01 M) in glacial acetic acid (10 mL), the appropriate aldehydes (0.01 M), namely, furfural or benzaldehyde was added. The reaction mixture was refluxed for 1 h., after cooling the separated solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

1-(6-Bromo-2-methylquinolin-4-yl)-2-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl-) hydrazine (6b)  

Yield: 82%, m.p.: > 300°C; IR (ν_{max}/cm^-1): 3206 (NH), 1637(C=N); 1H-NMR (CDCl_3, δ, ppm): 2.4 (s, 3H, CH_3), 6.3 (s, 1H, Ar, H-3), 6.7-7.8 (m, 6H, 5 Ar-H and N=CH), 8.1 (s, 1H, Ar, H-5) 9.3 (s, 1H, NH); 13C-NMR (CDCl_3, δ, ppm): 24.01 (CH_3), 107.2, 109.3, 109.8, 117.5, 118.4, 129.03, 132.8, 133.6, 133.9 142.8, 146.9, 149.4, 148.3, 158.8 (Ar-C, C=N); MS: m/z (%): 329, 331 (M^+, M^2, 26.2, 23.8) consistent with the molecular formula (C_{17}H_{14}BrN_O_9).
**1-(6-Bromo-2-methylquinolin-4-yl)-4-phenylthiosemicarbazide (8b)**

Yield: 85%, m.p.: 200°C; IR (ν\textsubscript{max}/cm\textsuperscript{-1}): 3260, 3168 (NH), 1652 (C=N); 1H-NMR (CDCl\textsubscript{3}, δ, ppm): 2.3 (s, 3H, quinaldine-CH\textsubscript{3}), 6.5 (s, 1H, H-3), 6.7 (d, J = 8.7, 2H, Ar, H-2',6'), 7.6-8.1 (m, 6H, Ar), 8.3 (s, 1H, NH), 9.8 (s, 1H, NH); 13C-NMR (CDCl\textsubscript{3}, δ, ppm): 24.2 (quinaldine-CH\textsubscript{3}), 110.71, 116.92, 117.6, 120.6, 129.2, 132.4, 136.8, 146.6, 147.4, 158.5 (Ar-C, C=N); 175.5 (C=O); MS; m/z (%): 324, 326 (M\textsuperscript{+}, 15.5, 16.8) consistent with the molecular formula (C\textsubscript{17}H\textsubscript{15}BrN\textsubscript{4}S).

**1-[6-Bromo-2-methylquinolin-4-yl]-4-ethyldenebenzenamine-1-hydrazono]-3-phenylthiazolidin-4-one (12b)**

To a solution of the thiosemicarbazide derivatives 10a, b (0.01 M) in absolute ethanol (15 mL), ethyl bromoacetate (0.01 M) was added and the mixture was heated under reflux for 3 h. After cooling the solid formed was collected by filtration, and recrystallized from dil. ethanol.

**2-[6-Bromo-2-methylquinolin-4-yl]-4-ethyldenebenzenamine-1-hydrazono]thiazolidin-4-one (12a)**

Yield: 77%, m.p.: 210°C; IR (ν\textsubscript{max}/cm\textsuperscript{-1}): 3260, 3168 (NH), 1652 (C=N); 1H-NMR (CDCl\textsubscript{3}, δ, ppm): 2.02 (s, 3H, CH\textsubscript{3}), 2.3 (s, 3H, quinaldine-CH\textsubscript{3}), 3.9 (s, 2H, thiazolidinone), 6.2 (s, 1H, H-3), 7.0 (d, J = 7.8, 2H, Ar, H-2', 6'), 7.6-7.9 (m, 4H, Ar-H), 8.1 (s, 1H, Ar, H-5), 9.5 (s, 1H, NH), 9.8 (s, 1H, NH); 13C-NMR (CDCl\textsubscript{3}, δ, ppm): 19.3 (CH\textsubscript{3}), 24.2 (quinaldine-CH\textsubscript{3}), 31.2 (CH\textsubscript{3}), 107.3, 109.5, 116.01, 116.04, 118.1, 120.8, 123.6, 126.01, 127.5, 127.9, 129.3, 129.9, 132.6, 143.02, 144.6, 147.3, 157.9, 159.2, 162.1 (Ar-C, C=N); MS; m/z (%): 467, 469 (M\textsuperscript{+}, 17.6, 16.8) consistent with the molecular formula (C\textsubscript{27}H\textsubscript{22}BrN\textsubscript{5}S).
m/z (%): 543, 545 (M⁺, M⁺², 29.8, 28.1) (C₂₇ H₂₂ Br N₅ O S).

1-[6-Bromo-2-methylquinolin-4-ylamino]-4-phenylethylidene semicarbazide (13)

A mixture of semicarbazide hydrochloride (0.01 M), and crystalline sodium acetate in water (10 mL) was added while stirring to a solution of compound 9 (0.001 M) in ethanol (20 mL). Stirring was continued for 15 min, at 5°C, the solid product was filtered off, washed with water, dried and recrystallized from ethanol.

Yield: 90%, m.p.: 275°C; IR (νmax/cm⁻¹): 3413 (NH₂), 3276 (br, 2NH), 1680 (C=O); 1H-NMR (CDCl₃, δ, ppm): 2.1 (s, 3H, CH₃), 2.3 (s, 3H, quinaldine-CH₃), 6.07 (s, 1H, NH₂), 6.3 (s, 1H, H-3), 6.6 (d, J = 8.7, 2H, H-2í, 6í), 6.9-8.1 (m, 5H, Ar-H), 9.04 (s, 1H, NH), 10.2 (s, 1H, NH); 13C-NMR (CDCl₃, δ, ppm): 22.5 (CH₃), 24.2 (quinaldine-CH₃), 107.3, 116.01, 116.4, 118.1, 120.8, 123.6, 129.9, 132.6, 144.5, 147.3, 157.9, 160.2, 161.7, 162.1 (Ar-C, C=N and C=O), MS; m/z (%): 411, 413 (M⁺, M⁺², 24.5, 23.0) consistent with the molecular formula (C₁₉H₁₈BrN₅O).

4-[6-Bromo-2-methylquinolin-4-yl)-(1, 2, 3-thiadiazol-4-yl) benzenamine (14a)

To a stirred solution of the semicarbazide 13 (0.001 M) in acetic acid (2 mL), at zero °C, thionyl chloride (0.025 M) was added dropwise and the resulting mixture was further stirred for 30 min at this temperature, then, the reaction mixture was left at room temperature overnight, and a saturated solution of sodium bicarbonate was added. The product was extracted with chloroform (40 mL), the organic layer was washed well with water, dried with anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the solid formed was filtered off, dried and recrystallized from DMF affording the title compound.

N-[4-(1, 2, 3-thiadiazol-4-yl) phenyl]-6-bromo-2-methylquinolin-4-amine (14a)

Yield: 89%, m.p.: > 300°C; IR (νmax/cm⁻¹): br. 3310 (NH), 1700 (C=O), 1630 (C=N); 1H-NMR (CDCl₃, δ, ppm): 2.3 (s, 3H, quinaldine-CH₃), 6.3 (s, 1H, H-3), 7.5-8.2 (m, 8H, Ar-H) 13C-NMR (CDCl₃, δ, ppm): 24.2 (quinaldine-CH₃), 24.6 (CH₂), 107.3, 116.4, 118.1, 120.8, 123.6, 126.5, 128.01, 129.3, 131.4, 132.6, 144.7, 147.3, 158.02 (Ar-C, C=N), 164.1 (C=O), MS; m/z (%): 293, 295 (M⁺, M⁺²), 10.7, 7.8 consistent with the molecular formula (C₁₇H₁₄BrN₃O).
8-Bromo-2,4-dimethyl-1H-imidazo[4,5-c]quinoline (16a), 8-bromo-4-methyl-2-phenyl-1H-imidazo[4,5-c]quinoline (16b)

A mixture of compounds 15a, b (0.01 M) and acetic acid (25 mL) was refluxed for 3 h. The reaction mixture was evaporated under reduced pressure, after cooling, the reaction mixture was poured onto ice-water and the solid formed was washed with water during filtration, dried and recrystallized from ethanol.

8-Bromo-2,4-dimethyl-1H-imidazo[4,5-c]quinoline (16a)

Yield: 69%, m.p.: 195 °C; IR (νmax/cm−1): 3231 (NH), 1591 (C=N); 1H-NMR (CDCl3, δ, ppm): 2.2 (s, 3H, CH3), 2.4 (s, 3H, quinaldine-CH3), 7.6-8.1 (m, 3H, Ar), 9.2 (s, 1H, NH) 13C-NMR (CDCl3, δ, ppm): 19.1(CH3), 21.2 (quinaldine-CH3), 119.6, 120.9, 121.9, 122.7, 126.1, 127.6, 129.01, 132.5, 142.6, 145.8, 158.9, 158.9, 158.9 (Ar-C, C=N); MS; m/z (%): 275, 277 (M+, M+2, 50.7, 21.9) consistent with the molecular formula (C12 H10 Br N3).

8-Bromo-4-methyl-2-phenyl-1H-imidazo[4,5-c]quinolone (16b)

Yield: 70%, m.p.: 154 °C; IR (νmax/cm−1): 3316 (NH), 1627 (C=N); 1H-NMR (CDCl3, δ, ppm): 2.4 (s, 3H, quinaldine-CH3), 7.1-7.9 (m, 7H, Ar), 8.1 (s, 1H, Ar-H9), 9.2 (s, 1H, NH), 13C-NMR (CDCl3, δ, ppm): 21.2 (CH3), 119.6, 120.9, 121.9, 124.4, 126.1, 127.6, 127.9, 128.04, 129.01, 132.9, 142.6, 145.8, 158.9 (Ar-C, C=N); MS; m/z (%): 337, 339 (M+, M+2, 5.5, 5.0) consistent with the molecular formula (C17 H12 Br N3).

5-Amino-1-(6-bromo-2-methylquinolin-4-yl)-1H-pyrazole-4-carbonitrile (17)

To a solution of compound 5 (0.01 M) in absolute ethanol (15 mL), 2-(ethoxymethylene) malononitrile (0.02 M) was added, the reaction mixture was heated under reflux for 3 h., the excess solvent was evaporated under reduced pressure, after cooling, the solid formed was filtered off, dried and recrystallized from ethanol.

Yield: 90 %, m.p.: >300 °C; IR (νmax /cm−1): 3412 (NH3), 2219 (CN); 1H-NMR (CDCl3, δ, ppm): 2.3 (s, 3H, CH3), 4.01 (s, 1H, NH), 6.9 (s, 1H, H-3), 7.3 (s, 1H, pyrazole), 7.5-8.1 (m, 3H, Ar) 13C-NMR (CDCl3, δ, ppm): 21.1 (CH3), 91.5, 111.7, 115.9, 119.6, 125.8, 127.1, 127.9, 130.4, 140.5, 142.7, 143.1, 147.9, 157.1 (Ar-C, C=N); MS; m/z (%): 327, 329 (M+, M+2, 31.8, 28.4) consistent with the molecular formula (C14 H10 Br N5).

1-(6-Bromo-2-methylquinolin-4-yl)-4,5-dihydro-4-oxo-1H-pyrazolo[3,4-d]pyrimidine-6-carbonyl chloride (18)

To a mixture of compound 17 (0.01 M) in dry benzene (15 mL) oxalyl chloride (0.015 M) was added. The mixture was stirred at room temperature for 24 h., the solid product was collected by filtration, washed well with water, dried and recrystallized from ethanol.

Yield: 88%, m.p.: 288°C; IR (νmax/cm−1): 3215 (NH), 1723, 1675 (2C=O); 1H-NMR (CDCl3, δ, ppm): 2.3 (s, 3H, Ar-CH3), 6.9 (s, 1H, H-3), 7.5-8.1 (m, 4H, 3Ar and 1H, pyrazole), 8.9 (s, 1H, NH), 13C-NMR (CDCl3, δ, ppm): 24.1(CH3), 106.3, 111.7, 112.9, 119.6, 127.1, 127.9, 130.4, 132.5, 140.9, 146.7, 147.9, 158.1, 159.9 (Ar-C, C=N); MS; m/z (%): 417, 419 (M+, M+2, 4.4, 6.1) consistent with the molecular formula (C16 H9 Br Cl N5O2).

Antimicrobial evaluation

Some of the synthesized new compounds were investigated for their antimicrobial effect toward each of Gram positive as well as Gram negative bacteria and fungi. Strains used to detect the antimicrobial activity of the prepared compounds included, Staphylococcus aureus ATCC 29213 and Bacillus subtilis ATCC 3366 as Gram positive, Pseudomonas aeruginosa ATCC 27853, Escherichia coli ATCC 25922, Salmonella typhi ATCC 25566 and Klepsiella pneumoniae ATCC 13883 as Gram negative, as well as Candida albicans NRRL Y-477 to present fungus.

The agar dilution method was used to study the microbiological inhibition of the prepared compounds. The Mueller–Hinton agar plates were prepared and adjusted to contain serial twofold dilutions of the tested compounds in-house. Each plate was inoculated with a specific microorganism at 0.5 McFarland and incubated at 37°C 24 h for.

The MIC was considered the lowest concentration of an antimicrobial agent that completely inhibited growth on the agar as detected visually. Ciprofloxacin and fluconazole were used as reference drugs.

CONCLUSION

The most common powerful quinoline derivatives as antibiotics are fluoroquinolones. However, literature survey reported that most of them have adverse effects which may occur almost anywhere in the body. Depending upon the above knowledge and in continuation to our previous efforts dealing
with the synthesis of various 6-bromoquinaldine derivatives of strong antimicrobial potency, a novel series of bromoquinaldine derivatives incorporated into or fused to various biologically active heterocyclic ring systems or glycosides were synthesized and evaluating some of them as antibacterial and antifungal. All the tested compounds exhibited potential antibacterial activity against Gram-positive bacteria except compound 6a which appeared to have activity against the Gram negative K. pneumoniae. From that we can conclude that substituted quinaldine compounds may provide more activity by further study trying to modify their substitutions to give new derivatives with expected improved antimicrobial activity and that may be the subject of our future work.

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REFERENCES


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