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Research Article

Synthesis and In Vitro Antibacterial Evaluation of Schiff Bases Derived FROM 2-Chloro-3-Quinolinecarboxaldehyde

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Abstract

Background: Design, identification, and synthesis of new antimicrobial agents along with preventive proceedings are essential to confront antibiotic-resistant pathogenic bacteria. Heterocyclic Schiff bases are biologically important compounds whose antimicrobial potentials have been proven to bacterial and fungal pathogens.

Objectives: In this study, some quinoline Schiff bases were synthesized from condensation of 2-chloro-3-quinolinecarboxaldehyde and aniline derivatives. Their inhibitory activities were evaluated against 6 gram-positive and 2 gram-negative bacterial pathogens.

Methods: Disc diffusion, broth microdilution, and time-kill tests were applied according to the CLSI guidelines to determine IZD, MIC, and MBC values.

Results: 2-Chloro-3-quinolinecarboxaldehyde Schiff bases could inhibit the growth of bacteria with IZDs of 7.5-19.8 mm, MICs of 256-2048 µg mL-1, and MBCs of 512 to ≥2048 µg mL-1.

Conclusion: Moderate antibacterial effects were observed with heterocyclic Schiff bases. Complexation and structural changes can improve their antimicrobial properties.

Keywords: Antibacterial effect, Broth microdilution, Disc diffusion, In vitro study, Quinoline Schiff base, Time-kill

Background

Schiff bases are organic compounds that contain imine or azomethine (C=NR) group and are often produced from condensation of aldehydes or ketones with primary aliphatic/aromatic amines. Quinoline Schiff bases are formed if either or both of the reaction participants possess quinoline ring. Quinoline nucleus is an essential part of the chemical structure of natural products, and pharmaceutical and biologically active compounds (Figure 1). Quinoline Yellow WS is a water-soluble greenish yellow food additive which is derived from the dye Quinoline Yellow SS (1). Bosutinib as a tyrosine kinase agonist is prescribed to treat Philadelphia chromosome-positive leukemia (2). Furthermore, Apomorphine as a morphine derivative, dopamine D2 inhibitor, and emetic agent has been used in the treatment of acute poisoning and parkinsonism (3). Mefloquine is an effective antimalaria drug against *Plasmodium falciparum* parasite (4). Imiquimod acts as an immune response modifier and helps to treat genital and anal warts, actinic keratoses, and superficial basal cell carcinoma (5). Cinchocaine or dibucaine is a surface anesthetic with high toxicity that has been restricted to spinal anesthesia (6).

Schiff bases are suitable multidentate ligands for metal complexation. The therapeutic potential of both coordinated and uncoordinated forms has been proven against pathogenic bacteria (7), fungi (8), viruses (9), protozoa (10), and helminths (11). In addition, quinolones are highly bioavailable antibiotics with a diverse range of activities and functions that are used to treat respiratory and urinary tract infections. The antibiotic examples of current quinolones and fluoroquinolones are as follows: moxifloxacin, lomefloxacin, gatifloxacin, norfloxacin, ofloxacin, nalidixic acid, rosoxacin, and ciprofloxacin. Mallandur et al synthesized some quinoline- and benzimidazole-based Schiff bases; their antibacterial effects were assessed against *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhi* via disc diffusion and

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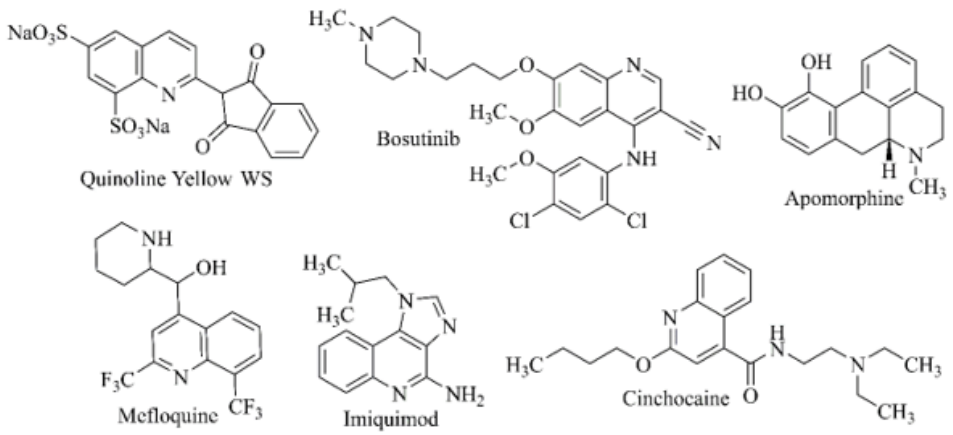


Figure 1. Selected Examples of Biologically Active Compounds Containing Quinoline Ring.

broth microdilution methods (12). Schiff bases of 2,6-disubstituted quinoline-3-carbaldehyde and their zinc and copper complexes were synthesized by Mandewale et al as potential aurora kinase (essential serine/threonine kinases for cell proliferation) inhibitors (13). Antimicrobial activities of 2-sulfanyl or 2-hydroxyquinoline-3-carbaldehyde Schiff bases and their corresponding copper (II), cobalt (II), zinc (II), and nickel (II) complexes were evaluated on *E. coli* and *S. aureus* by zone of inhibition method (14). The inhibitory activities of two Schiff bases derived from 2-chloroquinoline-3-carbaldehyde were also investigated on *Bacillus cereus*, *S. aureus*, *Pseudomonas aeruginosa*, and *E. coli* (15).

Other methods were proposed to synthesize imines besides the reaction of aldehydes/ketones and amines. The acid-catalyzed interaction of hydrazoic acid with tertiary alcohols to afford imines is referred to as the Schmidt reaction (16). The *in situ* oxidation of primary alcohols to corresponding aldehydes catalyzed by *N*-heterocyclic carbene (NHC)-silver (I) complexes (17), manganese dioxide (18), palladium (19), *ortho*-naphthoquinone (20), and ferric nitrate (21) has produced imines in good yields. The retro-aza-Henry-type reaction of amines with nitrostyrenes (22), intermolecular alkyne hydroamination (23), Pd-catalyzed reaction of aryl halides, and bulky arylamines (24) were also developed for this purpose.

In order to expand potential antimicrobial agents, the inhibitory activity of some synthesized Schiff bases of 2-chloro-3-quinolinecarboxaldehyde was evaluated against the pathogenic genera *Rhodococcus*, *Streptococcus*, *Staphylococcus*, *Enterococcus*, *Bacillus*, *Shigella,* and *Proteus*.

Subjects and Methods

Chemicals

All reagents were prepared from reputable chemical companies. The uncorrected melting points were determined by Kruss KSP1N melting point apparatus. Aluminum TLC plates (20×20 cm) containing silica gel coated with fluorescent indicator F254 were used to monitor the progress of reactions. Bruker Tensor-27 FT-IR spectrometer was applied to record the FT-IR spectra of compounds. ^{1}H and ^{13}C NMR spectra were registered using a Bruker 400 MHz-NMR spectrometer.

Synthesis of 2-chloroquinoline-3-carbaldehyde (2)

A total of 120 mmol phosphoryl chloride (18.36 g) was gradually added to 10 mmol acetanilide (**1**, 1.34 g) and 30 mmol dry DMF (2.30 mL) at 0-5°C (21). The solution was warmed to 90°C, and stirred under these conditions for 16 hours. The contents of reaction were cooled to the room temperature, and poured into 100 g crashed ice. The precipitate was filtered and washed with water. The solid was recrystallized from acetonitrile to achieve a yield of 90% (1.97 g) of pure white compound **2**.

General Procedure for the Synthesis of Quinoline Schiff Bases 4a-g

A solution of 1 mmol aniline derivatives **3a-g** in 5 mL ethanol was added dropwise to a solution containing 1 mmol 2-chloroquinoline-3-carbaldehyde (**2**) at room temperature. The mixture was refluxed for 3-7 hours. The progress of the reaction was checked by TLC, including a mixture of ethyl acetate-hexane (2: 1). The precipitate was then filtered off, washed with ethanol, and recrystallized from appropriate solvent to give Schiff bases **4a-g** as yellow solids.

(E)-1-(2-Chloroquinolin-3-yl)-N-phenylmethanimine (4a)

IR (KBr) ν: 2924 (C-H), 1647 (C=N), 1490, 1324 (C-N), 1044, 752 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (s, 1H, Ar-H-4), 8.90 (s, 1H, CH=N), 8.20 (d, J = 8.1 Hz, 1H, Ar-H-5), 8.02 (d, J = 7.9 Hz, 1H, Ar-H-8), 7.91 (m, 1H, Ar-H-7), 7.74 (m, 1H, Ar-H-6), 7.61 (m,

2H, Ph-H-2′,6′), 7.16-7.11 (m, 3H, Ph-H-3′,4′,5′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 122.6 (Ph-C-2′,6′), 127.0 (Ph-C-4′), 127.9 (Ar-C-4a), 128.1 (Ar-C-6), 128.3 (Ar-C-8), 129.7 (Ar-C-5), 130.1 (Ph-C-3′,5′), 131.6 (Ar-C-7), 137.4 (Ar-C-4), 147.1 (Ph-C-1′), 148.2 (Ar-C-8a), 149.5 (Ar-C-2), 155.7 (CH=N) ppm.

(*E*)-1-(2-Chloroquinolin-3-yl)-*N*-(4-methoxyphenyl) methanimine (**4b**)

IR (KBr) ν: 2925 (C-H), 1615 (C=N), 1507, 1405, 1300 (C-N), 1248 (C-O), 1163, 1030, 822, 776, 752, 519 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (s, 1H, Ar-H-4), 8.96 (s, 1H, CH=N), 8.27 (d, *J* = 7.7 Hz, 1H, Ar-H-5), 8.02 (d, *J* = 8.4 Hz, 1H, Ar-H-8), 7.91 (m, 1H, Ar-H-7), 7.73 (m, 1H, Ar-H-6), 7.44 (d, *J* = 8.9 Hz, 2H, Ph-H-2′,6′), 7.05 (d, *J* = 8.9 Hz, 2H, Ph-H-3′,5′), 3.82 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.8 (CH_3), 115.0 (Ph-C-3′,5′), 123.3 (Ph-C-2′,6′), 127.3 (Ar-C-3), 127.9 (Ar-C-4a), 128.1 (Ar-C-6), 128.3 (Ar-C-8), 129.8 (Ar-C-5), 132.7 (Ar-C-7), 138.1 (Ar-C-4), 142.2 (Ph-C-1′), 148.0 (Ar-C-8a), 149.8 (Ar-C-2), 158.9 (Ph-C-4′), 159.1 (CH=N) ppm.

(*E*)-2-(((2-Chloroquinolin-3-yl) methylene) amino) phenol (**4c**)

IR (KBr) ν: 3337 (OH stretching), 2921 (C-H), 2757, 2716, 2586, 1613 (C=N), 1570, 1515, 1485, 1397, 1359 (OH bending), 1327 (C-N), 1289, 1209, 1170, 1134, 1050, 963, 927, 874, 686, 596, 510 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.79 (br, 1H, OH), 9.39 (s, 1H, Ar-H-4), 9.10 (s, 1H, CH=N), 8.21 (d, *J* = 7.7 Hz, 1H, Ar-H-5), 8.03 (d, *J* = 8.5 Hz, 1H, Ar-H-8), 7.92 (m, 1H, Ar-H-7), 7.74 (m, 1H, Ar-H-6), 7.33 (m, 1H, Ph-H-4′), 7.18 (m, 1H, Ph-H-6′), 6.98 (m, 1H, Ph-H-5′), 6.918 (m, 1H, Ph-H-3′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.8 (Ph-C-6′), 119.9 (Ph-C-3′), 120.3 (Ph-C-5′), 127.3 (Ar-C-3), 127.9 (Ar-C-4a), 128.9 (Ph-C-4′), 128.2 (Ar-C-6), 128.3 (Ar-C-8), 129.6 (Ar-C-5), 132.6 (Ar-C-7), 137.5 (Ph-C-1′), 138.6 (Ar-C-4), 148.1 (Ar-C-8a), 149.8 (Ar-C-2), 152.0 (Ph-C-2′), 154.3 (CH=N) ppm.

(*E*)-1-(2-Chloroquinolin-3-yl)-*N*-(*p*-tolyl)methanimine (**4d**)

IR (KBr) ν: 2923 (C-H), 1622 (C=N), 1573, 1507, 1488, 1396, 1325 (C-N), 1144, 1048, 922, 812, 775, 748, 518 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (s, 1H, Ar-H-4), 8.93 (s, 1H, CH=N), 8.26 (d, *J* = 7.7 Hz, 1H, Ar-H-5), 8.02 (d, *J* = 8.4 Hz, 1H, Ar-H-8), 7.91 (m, 1H, Ar-H-7), 7.72 (m, 1H, Ar-H-6), 7.30 (dd, *J* = 3.4 Hz, 4H, Ph-H-2′,3′,5′,6′), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.1 (CH_3), 121.6 (Ph-C-2′,6′), 127.2 (Ar-C-3), 127.6 (Ar-C-4a), 128.1 (Ar-C-6), 128.3 (Ar-C-8), 129.8 (Ar-C-5), 130.3 (Ph-C-3′,5′), 132.7 (Ar-C-7), 136.9 (Ph-C-4′), 138.1 (Ar-C-4), 148.1 (Ph-C-1′), 148.6 (Ar-C-8a), 149.8 (Ar-C-2), 154.9 (CH=N) ppm.

(*E*)-1-(2-Chloroquinolin-3-yl)-*N*-(*m*-tolyl)methanimine (**4e**)

IR (KBr) ν: 2927 (C-H), 1611 (C=N), 1583, 1488, 1376, 1352, 1330 (C-N), 1223, 1168, 1134, 1112, 1054, 958, 941, 930, 878, 852, 822, 781, 754, 718, 689, 627, 595, 525, 481, 458 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.17 (s, 1H, Ar-H-4), 8.83 (s, 1H, CH=N), 8.29 (d, *J* = 7.5 Hz, 1H, Ar-H-5), 8.03 (d, *J* = 8.5 Hz, 1H, Ar-H-8), 7.93 (m, 1H, Ar-H-7), 7.74 (m, 1H, Ar-H-6), 7.31 (d, *J* = 7.3 Hz, 1H, Ph-H-5′), 7.28 (d, *J* = 7.4 Hz, 1H, Ph-H-4′), 7.23 (m, 1H, Ph-C-6′), 7.15 (d, *J* = 7.7 Hz, 1H, Ph-H-2′), 2.39 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.1 (CH_3), 118.3 (Ph-C-6′), 127.0 (Ph-C-2′), 127.3 (Ph-C-4′), 127.5 (Ar-C-3), 127.7 (Ar-C-4a), 128.2 (Ar-C-6), 128.4 (Ar-C-8), 129.9 (Ar-C-5), 130.8 (Ph-C-5′), 132.2 (Ar-C-7), 132.9 (Ph-C-3′), 138.5 (Ar-C-4), 148.2 (Ph-C-1′), 149.8 (Ar-C-8a), 150.4 (Ar-C-2), 155.5 (CH=N) ppm.

(*E*)-*N*-(4-Chlorophenyl)-1-(2-chloroquinolin-3-yl) methanimine (**4f**)

IR (KBr) ν: 2923 (C-H), 1642 (C=N), 1543, 1487, 1333 (C-N), 1089, 536 (C-Cl) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.18 (s, 1H, Ar-H-4), 8.94 (s, 1H, CH=N), 8.28 (d, *J* = 8.8 Hz, 1H, Ar-H-5), 8.03 (d, *J* = 9.3 Hz, 1H, Ar-H-8), 7.93 (m, 1H, Ar-H-7), 7.74 (m, 1H, Ar-H-6), 7.53 (d, *J* = 2.1 Hz, 2H, Ph-H-3′,5′), 7.43 (d, *J* = 2.1 Hz, 2H, Ph-H-2′,6′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 123.5 (Ph-C-2′,6′), 127.2 (Ar-C-3), 127.4 (Ar-C-4a), 128.1 (Ar-C-6), 128.4 (Ar-C-8), 129.1 (Ar-C-5), 129.8 (Ph-C-3′,5′), 133.0 (Ph-C-4′), 132.7 (Ar-C-7), 138.5 (Ar-C-4), 141.8 (Ph-C-1′), 148.3 (Ar-C-8a), 150.0 (Ar-C-2), 157.0 (CH=N) ppm.

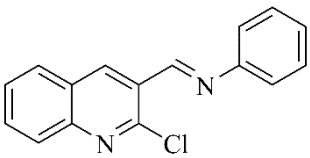
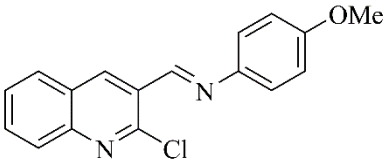
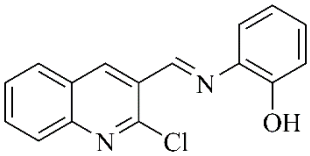
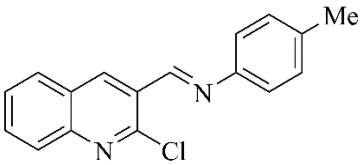
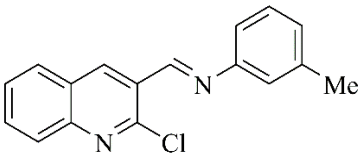
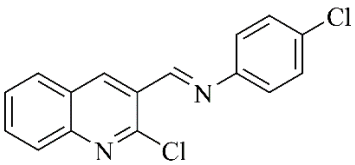
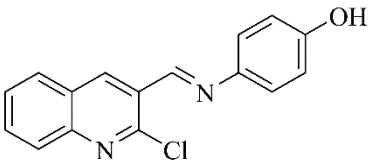
(*E*)-4-(((2-Chloroquinolin-3-yl) methylene)amino) phenol (New compound) (**4g**)

IR (KBr) ν: 3064 (OH stretching), 2929 (C-H), 1614 (C=N), 1583, 1505, 1449, 1359 (OH bending), 1329 (C-N), 1275, 1230, 1165, 1139, 1111, 1048, 963, 935, 833, 748, 600, 547, 477 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73 (s, 1H, OH), 9.12 (s, 1H, Ar-H-4), 8.95 (s, 1H, CH=N), 8.27 (d, *J* = 7.3 Hz, 1H, Ar-H-5), 8.02 (d, *J* = 8.1 Hz, 1H, Ar-H-8), 7.91 (m, 1H, Ar-H-7), 7.73 (m, 1H, Ar-H-6), 7.35 (d, *J* = 8.7 Hz, 2H, Ph-H-2′,6′), 6.87 (d, *J* = 8.7 Hz, 2H, Ph-H-3′,5′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 116.3 (Ph-C-3′,5′), 123.4 (Ph-C-2′,6′), 127.3 (Ar-C-3), 128.0 (Ar-C-4a), 128.1 (Ar-C-6), 128.3 (Ar-C-8), 129.7 (Ar-C-5), 132.5 (Ar-C-7), 137.6 (Ar-C-4), 142.5 (Ph-C-1′), 147.9 (Ar-C-8a), 149.8 (Ar-C-2), 152.1 (Ph-C-4′), 157.7 (CH=N) ppm.

Antibacterial Susceptibility Testing

Mueller-Hinton broth (MHB) and Mueller-Hinton agar (MHA) as bacterial growth media were prepared from HiMedia Company. Antibiotic and sterile blank discs (6 mm diameter) were respectively purchased from Sigma-Aldrich and Padtan Teb Companies. Gram-positive strains including *Staphylococcus epidermidis* (PTCC 1435), *Rhodococcus equi* (PTCC 1633), *Enterococcus faecalis* (PTCC 1778), *Staphylococcus aureus* (PTCC

Table 1. The Chemical Structure of Quinoline Schiff Bases

Entry	Product		Ar	Yield (%)	M. P. (°C)	
					Found	Lit. (Ref.)
1		**4a**	C_6H_5	70	133-135	128-130 (27)
2		**4b**	4-CH_3O-C_6H_4	95	176-178	175 (28)
3		**4c**	2-HO-C_6H_4	85	184-185	180 (29)
4		**4d**	4-H_3C-C_6H_4	80	191-193	194 (28)
5		**4e**	3-H_3C-C_6H_4	80	154-156	- (30)
6		**4f**	4-Cl-C_6H_4	65	199-201	204 (28)
9		**4g**	4-HO-C_6H_4	95	158-160	-

1189), *Bacillus subtilis* subsp. *spizizenii* (PTCC 1023), *Streptococcus pneumoniae* (PTCC 1240), and gram-negative strains including *Shigella flexneri* (PTCC 1234) and *Proteus vulgaris* (PTCC 1079) were purchased from the Persian Type Culture Collection. The 0.5 McFarland standard bacterial suspensions (1.5×10^8 CFU mL^{-1}) were initially prepared in MHB using a UV-2100 RAYLEIGH double beam UV-Vis spectrophotometer. All results are as the average of three independent tests.

Measurement of Inhibition Zone Diameter

The disk-diffusion method was used for the measurement of inhibition zone diameter (IZD) values according to the CLSI (Clinical and Laboratory Standards Institute) M02-A11 guideline (26). In this respect, 3 colonies of initial suspensions were inoculated on MHA plates (100 mm) by a swab, and 5 sterile blank discs were included on inoculated media. Then, 10 µL of compounds (10240 µg mL^{-1}) and/or antibiotic (17.6 µg mL^{-1}) were moved onto the dedicated discs. They were incubated at 37°C for 18 hours. The IZD values were measured in millimeter using caliper.

Determining the Minimum Inhibitory Concentration

The broth microdilution method was adopted for the determination of minimum inhibitory concentration (MIC) values according to the following CLSI M07-A9 guideline (26): 20 µL of derivatives were dissolved in

DMSO (20480, 10240, 5120, 2560, 1280, 640, 320, 160 µg mL^{-1}) or aqueous solution of antibiotic (80, 40, 20, 10, 5, 2.5, 1.25, 0.63), and 80 µL of MHB medium and 100 µL of bacterial suspensions diluted 300 times (5×10^5 CFU mL^{-1}) were added to all wells of an eight-row, 96-well, round-bottom microplate. They were incubated for 20 hours at 37°C with a shaking speed of 100 rpm. The MIC value was determined as the lowest concentration of derivatives or antibiotic without any visible bacterial growth.

Table 2. Optimization of the Model Reaction Conditions for the Preparation of Schiff Base 4a

Entry	Solvent	Time (h)	Yield (%)
1	MeOH	5	40
2	EtOH	5	70
3	CH_3CN	12	30
4	DMF	10	60
5	*n*-Hexane	12	Trace

Determining the Minimum Bactericidal Concentration

The time-kill test was performed for the determination of minimum bactericidal concentration (MBC) values according to the following CLSI M26-A guideline (26): samples of all microwells without turbidity in the previous experiment were cultured using a swab in plates containing MHA medium. They were incubated for 24 hours at 37°C. The lowest concentration of derivatives or antibiotic in which bacteria could not survive was considered as the MBC value.

Results

As shown in Scheme 1, quinoline Schiff bases **4a-g** were synthesized via condensation of 2-chloroquinoline-3-carbaldehyde (**2**) and aniline derivatives **3a-g** in the absence of any catalyst. The data are reported in Table 1.

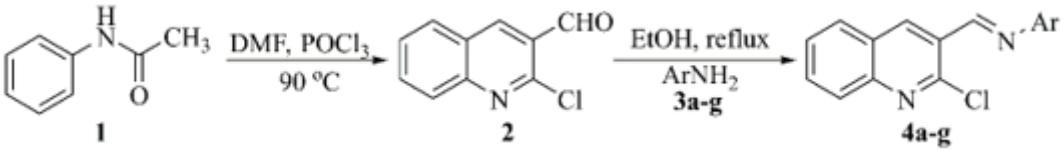
The reaction progress between 1 mmol of both quinoline **2** and aniline **3a** was checked in 5 mL of different solvents in thermal heating under reflux conditions. As shown in Table 2, the greatest amount of products were obtained in ethanolic solutions.

Moreover, the inhibitory activity of synthesized

Table 3. Antibacterial Activity of Quinoline Derivatives **2** and **4a-g**

Bacteria		Products								Antibiotic
		2	4a	4b	4c	4d	4e	4f	4g	CRO[d]
1633	IZD[a]	-	14.4±0.5	-	15.2±0.3	-	7.5±0.4	-	12.8±0.6	21.5±0.6
	MIC[b]	-	512	-	1024	-	2048	-	1024	2
	MBC[c]	-	1024	-	2048	-	>2048	-	2048	2
1240	IZD	9.4±0.3	-	-	-	-	-	-	9.8±0.1	-
	MIC	1024	-	-	-	-	-	-	2048	-
	MBC	2048	-	-	-	-	-	-	>2048	-
1435	IZD	-	-	-	15.7±0.5	10.2±0.7	10.6±0.2	-	14.0±0.4	18.5±0.3
	MIC	-	-	-	1024	256	1024	-	1024	0.5
	MBC	-	-	-	2048	512	2048	-	1024	2
1778	IZD	-	-	-	11.5±0.1	-	-	-	-	18.3±0.4
	MIC	-	-	-	2048	-	-	-	-	1
	MBC	-	-	-	>2048	-	-	-	-	2
1189	IZD	-	-	-	12.3±0.4	-	-	-	-	15.3±0.7
	MIC	-	-	-	512	-	-	-	-	4
	MBC	-	-	-	1024	-	-	-	-	16
1023	IZD	10.2±0.2	14.7±0.1	10.6±0.8	19.8±0.6	14.9±0.3	15.2±0.2	11.9±0.5	14.3±0.3	25.7±0.6
	MIC	1024	256	2048	256	1024	512	1024	1024	0.25
	MBC	2048	512	>2048	512	2048	1024	2048	2048	0.5
1234	IZD	-	-	-	17.6±0.4	12.7±0.2	9.8±0.2	14.3±0.5	11.5±0.1	34.1±0.5
	MIC	-	-	-	512	1024	2048	512	1024	2
	MBC	-	-	-	1024	2048	>2048	1024	2048	4
1079	IZD	-	-	-	-	-	-	-	11.2±0.2	-
	MIC	-	-	-	-	-	-	-	2048	-
	MBC	-	-	-	-	-	-	-	>2048	-

Note. [a] Values reported as mm, [b] Values reported as µg mL^{-1}, [c] Values reported as µg mL^{-1}, [d] Ceftriaxone, -: No noticeable antibacterial effect at initial concentrations.



Scheme 1. General Procedure for the Synthesis of Schiff Bases **4a-g**.

heterocycles **2** and **4a-g,** as well as antibiotic ceftriaxone were evaluated against a variety of pathogenic bacteria. The results are recorded as IZD, MIC, and MBC values in Table 3.

Discussion

In vitro antibacterial potentials of all synthesized heterocyclic derivatives were studied and compared with those of ceftriaxone. All of our synthesized heterocycles could inhibit the growth of *B. subtilis* subsp. *spizizenii*. The blocking effects against *E. faecalis* and *S. aureus* were observed with only quinoline Schiff base **4c** containing 2-hydroxyaniline substituent. The quinoline **4g** bearing 4-hydroxyaniline substituent was the only effective heterocycle and the only Schiff base derivative on gram-negative *Proteus vulgaris* and gram-positive *S. pneumoniae*, respectively. Moreover, the heterocyclic compounds **4c** and **4g** affected a wider range of tested bacterial strains. Schiff bases prepared by the condensation of 2-chloro quinoline-3-carbaldehyde derivatives and a substituted 5-benzimidazolecarboxylic hydrazide could inhibit *E. coli* strains with MICs in the range of 25 to 50 μg mL^{-1} (12). Cu (II) complexes of 2-sulfanyl or 2-hydroxyquinoline-3-carbaldehyde Schiff bases exhibited better antibacterial effects than their corresponding ligands (14). Furthermore, moderate antibacterial activities were observed with two synthesized Schiff bases based on 2-chloroquinoline-3-carbaldehyde (15). It has been found that quinolone and fluoroquinolone antibiotics block the growth of bacteria via enzyme inhibition (31). DNA gyrase and topoisomerase IV as DNA topology controllers are two essential enzymes produced by the most bacteria whose function is impaired in the presence of quinolones and fluoroquinolones. They also play a key role in the repair, deactivation, replication, and transcription of DNA. In addition, molecular docking studies predicted effective interactions of 6-chloro-2-hydroxyquinoline-3-carbaldehyde Schiff bases introduced into the active site of target protein (13).

Conclusion

To conclude, synthesized 2-chloroquinoline-3-carbaldehyde Schiff bases showed moderate inhibitory properties against some important pathogenic gram-negative and gram-positive strains. Changes in the structure and position of substituents on quinoline ring, complexation, and the use of new condensing primary amines and their equivalents may improve antimicrobial effects.

Authors' Contributions

HB supervised the synthetic and antibacterial parts and analyzed the microbial data. HHM synthesized title heterocycles. GB supervised the synthetic part and designed target compounds. RA analyzed the chemical data. MMM collaborated in antibacterial part.

Conflict of Interest Disclosures

No conflict of interests was declared by the authors.

Ethical Issues

All synthetic and biological tests were performed in accordance with the laws approved by the Ethics Committee of University of Zabol, Zabol, Iran.

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