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Research Article

NOVEL CHALCONE DERIVATIVES OF 3-HYDROXYQUINOXALINE-2-CARBOXALDEHYDE: SYNTHESIS, CHARACTERIZATION AND COMPARATIVE BIOLOGICAL SCREENING

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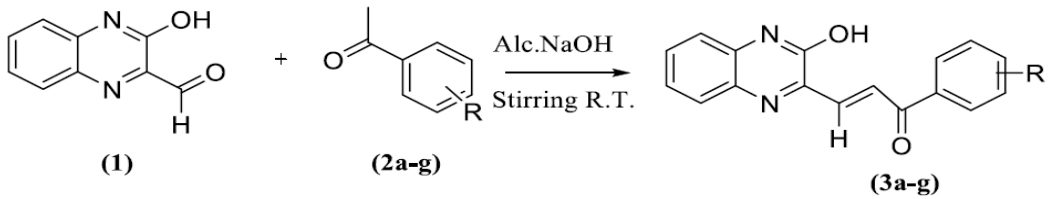
ABSTRACT
The Chalcones were prepared by condensation of 3-hydroxyquinoxaline-2-carboxaldehyde and substituted acetophenone in presence of alcoholic NaOH as base. The yield of all chalcone derivatives was found to be in the range of 68-80%. The purity of the compounds was ascertained by melting point and TLC. The synthesized compounds were characterized by using IR, ^{1}H NMR and MASS data together with elemental analysis. All the synthesized compounds were evaluated for their antibacterial activity against two gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) and two Gram-negative bacteria (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441) by using ampicillin, chloramphenicol and ciprofloxacin as the standard antibacterial drugs. All compounds shows very good to moderate activity.

Keywords: Quinoxaline, Chalcones, 3-hydroxyquinoxaline2-carboxaldehyde, Acetophenone.

1. INTRODUCTION
Quinoxaline [1] also known as 1, 4-benzodizine, benzopyridazine, phenpiazine or benzopyrazine is a heterocyclic compound in which a benzene ring is fused with pyrazine ring. Quinoxaline and its derivatives constitute an important class of nitrogen containing heterocycles. The presence of hetero atoms in their ring and extended π-conjugation causes decrease in columbic repulsion. Derivatives of Quinoxaline are widely used as bridging ligand in both homobimetallic and heterobimetallic complexes. They have wide variety of biological applications [2-9] including in optoelectronic devices [10-11] self extinguishing and flame resistance polymer, flourophores [12-15] photo sensitizers, corrosion inhibitor and electron transport material. Chalcone derivatives are used in various studies because of their vital role as precursor in the biosynthesis of flavonoids and other pharmacological important compounds. The chalcones explored as a new class of non-azo dyes [16] and they have displayed a broad spectrum of biological and pharmacological activities, among which antioxidant [17-19], antibacterial [20-22], antifungal [23-25], anti-cancer, anti-inflammatory [26-28] and antidepressant [29-30] activities as well as some compounds shows non-linear optical properties [31-32] and used as fluorescent probes [33]. The increasing interest in the field of 3-hydroxyquinoxaline-2-carboxaldehyde chemistry and continuation of our ongoing study [34] promoted us to synthesize some chalcone derivatives of 3-hydroxy-quinoxaline-2-carboxaldehyde. In this present study, a series of some new 3-hydroxyquinoxaline-2-carboxal-dehyde chalcone derivatives were synthesized by reacting 3-hydroxyquinoxaline-2-carboxaldehyde **(1)** with sub-stituted acetophenone **(2a-g)** in ethanolic solution of sodium hydroxide to yield substituted chalcone derivatives (3a-g) (Scheme 1).



R=H, 4-OH, 4-NH$_2$, 4-Br, 4-OMe, 4-Cl, 4F
Scheme: 1

The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, mass spectroscopy and elemental analysis. Literature survey reveals that chalcone derivatives shows good activity against microbes hence all synthesized compounds were evaluated for antimicrobial activity.

2. MATERIAL AND METHODS

2.1. Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Perkin-Elmer spectrometer.^{1}H NMR spectra were recorded on Bruker Advance II 400 spectrometer in $CDCl_3$ by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel 60F254 with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm). All reagents and solvents were purified and dried by standard techniques.

2.2. General procedure for the synthesis (E)-3-(3-hydroxyquinoxalin-2-yl)-1-substituted phenylprop-2-en-1-one (Chalcone) (3a-g)

A mixture of substituted acetophenone **(2a-g)** (0.01mol) and 3-hydroxyquinoxaline-2-carboxaldehyde (**1**) (0.01mol) was stirred in ethanol (30 ml) and then sodium hydroxide solution (15 ml, 0.02 mol) was added to it. The reaction mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The Chalcone *i.e.* (E)-3-(3-hydroxyquinoxalin-2-yl)-1-substituted phenyl-prop-2-en-1-one **(3a-g)** precipitated as solid. Then it was filtered, dried and purified by crystallization from acetic acid. Percentage yield and physical constants were recorded.

2.3. Antimicrobial Evaluation

The *in vitro* biological screening effects of the investigated compounds were tested against the bacteria: *staphylococcus aureus (*MTTC 96)*, Streptococcus pyogenes (*MTTC 443) (Gram positive) and *Escherichia coli (*MTTC 443)*, pseudomonas aerugenosa (*MTTC 441) (Gram negative) by disc diffusion method [35] using Mueller Hinton agar as the medium. The stock solution (100µg/ml) was prepared by dissolving the compounds in DMSO. In a typical procedure [36] well was made on the agar inoculated with microorganisms. The well was filled with the test solution using micropipette and plates were then kept in a refrigerator for 30-45 minutes and then incubated at 37°C for 18-24 hours. After incubation, diameter of zone of complete inhibition (Including diameter of the well) was measured in mm using an antibiotic zone reader.

3. RESULTS AND DISCUSSION

The structures of the synthesized compounds (**3a-g**) were confirmed on the basis of spectral and elemental analysis. Literature survey reveals that the synthesized pharmacologically active molecules *i.e.* (E)-3-(3-hydroxyquinoxalin-2-yl)-1-substituted phenylprop-2-en-1-one derivatives **(3a-g)** were not reported. The antimicrobial results revealed that the synthesized derivative possesses promising to moderate antibacterial activities.

3.1. Spectral data of synthesized compounds

3.1.1. (E)-3-(3-hydroxyquinoxalin-2-yl)-1-phenylprop-2-en-1-one (3a)

Pale yellow solid (238mg, yield 68%) mp 256-260°C; FT-IR (KBr) cm^{-1}: 3250, 3015, 1655, 1606, 1585, 1262; ^{1}HNMR (400MHz, $CDCl_3$): 10.48 (brs, 1H, OH), 9.52 (S, 1H, N=C-H), 8.25 (d, 2H, j= 8.3Hz, C3 & C5 phenyl ring), 8.1-8.14 (m, 4H, C5-C8 quinoxaline ring), 7.89 (dd, 2H, J=8.29Hz, C2 & C6 phenyl ring), 7.83 (d, 1H, J= 17.7 Hz, H-C=C-C=O), 6.94 (d, 1H, J= 17.7Hz, C=CH-C=O).

3.1.2. (E)-1-(4-hydroxyphenyl)-3-(3-hydroxy-quinoxalin-2-yl) prop-2-en-1-one (3b)

Pale yellow solid (238mg, yield 68%) mp 256-260°C; FT-IR (KBr) cm^{-1}: 3250, 3015, 1655, 1606, 1585, 1262; ^{1}HNMR (400MHz, $CDCl_3$): 10.48 (brs, 1H, OH), 9.52 (S, 1H, N=C-H), 8.25 (d, 2H, j= 8.3Hz, C3 & C5 phenyl ring), 8.1-8.14 (m, 4H, C5-C8 quinoxaline ring), 7.89 (dd, 2H, J=8.29Hz, C2 & C6 phenyl ring), 7.83 (d, 1H, J= 17.7 Hz, H-C=C-C=O), 6.94 (d, 1H, J= 17.7Hz, C=CH-C=O).

3.1.3. (E)-1-(4-aminophenyl)-3-(3-hydroxy-quinoxalin-2-yl) prop-2-en-1-one (3c)

Orange solid (245mg, yield 70%) mp 182-185°C; FT-IR (KBr) cm^{-1}: 3354, 3040, 1658, 1609, 1585; ^{1}HNMR (400MHz, $CDCl_3$) 9.48 (S, 1H, N=C-H), 7.98-8.30 (m, 4H, C5-8 quinoxaline ring), 7.96-8.01 (dd, 2H, J=8.60Hz, C2 & C6 phenyl ring), 7.81-7.86 (dd, 2H, J=8.62Hz, C3 & C5 phenyl ring), 7.80 (d, 1H,

j=17.30Hz, H-C=C-C=O), 6.71(d, 1H, J=17.30Hz, C=CH-C=O), 3.5 (brs, 2H, NH_2).

3.1.4. (E)-1-(4-bromophenyl)-3-(3-hydroxy-quinoxalin-2-yl) prop-2-en-1-one (3d)

Pale yellow solid (283mg, yield 80%) mp 126-130°C; FT-IR (KBr) cm^{-1}: 3100, 1685, 1580, 1489, 832; ^{1}HNMR (400MHz, $CDCl_3$) 9.68 (S, 1H, N=C-H), 7.85-8.35 (m, 4H, C5-8 quinoxaline ring), 7.65 (dd, 2H, J=8.65Hz, C2 & C6 phenyl ring), 7.79 (dd, 2H, J=8.60Hz, C3 & C5 phenyl ring), 7.23 (d, 1H, J=17.30Hz, H-C=C-C=O), 6.85(d, 1H, J=17.30Hz, C=CH-C=O).

3.1.5. (E)-3-(3-hydroxyquinoxalin-2-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (3e)

Pale yellow solid (273mg, yield 78%) mp 94-98°C; FT-IR (KBr) cm^{-1}: 3070, 1671, 1600, 1514, 1259; ^{1}HNMR (400MHz, $CDCl_3$) 9.39 (s, 1H, N=C-H), 7.86-8.34 (m, 4H, C5-8 quinoxaline ring), 7.88 (dd, 2H, J=8.3Hz, C2 & C6 phenyl ring), 7.02 (dd, 2H, J=8.3Hz, C3 & C5 phenyl ring), 7.25 (d, 1H, J=17.3Hz, H-C=C-C=O), 6.84(d, 1H, J=17.3Hz, C=CH-C=O); 3.85 (s, 3H, OCH_3).

3.1.6. (E)-1-(4-chlorophenyl)-3-(3-hydroxy-quinoxalin-2-yl) prop-2-en-1-one (3f)

Pale yellow solid (262mg, yield 75%) mp 124-126°C; FT-IR (KBr) cm^{-1}: 3095, 1683, 1588, 1493, 758; ^{1}HNMR (400MHz, $CDCl_3$) 9.30 (S, 1H, N=C-H), 7.86-8.35 (m, 4H, C5-C8 quinoxaline ring), 7.51 (dd, 2H, J=8.66Hz, C2 & C6 phenyl ring), 7.73 (dd, 2H, J=8.66Hz, C3 & C5 phenyl ring), 7.227 (d, 1H, J=17.69Hz, H-C=C-C=O), 6.84 (d, 1H, J=17.69Hz, C=CH-C=O).

3.1.7. (E)-1-(4-fluorophenyl)-3-(3-hydroxy-quinoxalin-2-yl) prop-2-en-1-one (3g)

Brown (204mg, yield 68%) mp 256-260°C; FT-IR (KBr) cm^{-1}: 3070, 1677, 1597, 1511, 685 ; ^{1}HNMR (400MHz, $CDCl_3$) 9.31(S, 1H, N=C-H), 7.86-8.33 (m, 4H, C5-C8 quinoxaline ring), 7.446 (dd, 2H, J=8.67Hz, C2 & C6 phenyl ring), 7.714 (dd, 2H, J= 8.67Hz, C3 & C5 phenyl ring), 7.251 (d, 1H, H-C=C-C=O), 6.84 (d, 1H, C=CH-C=O).

3.2. Antimicrobial activity

All the synthesized compounds were evaluated for their antibacterial activity against two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) and two Gram-negative bacteria (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441) by using ampicillin, chloramphenicol and ciprofloxacin as the standard antibacterial drugs. The antibacterial screening of compound **[3a-3g]** pointed out that in Gram-positive bacteria, compounds **3b** (MIC=100μg/ml) showed an outstanding inhibitory effect against *Staphylococcus aureus* as compared to ampicillin (MIC=250μg/ml) and admirable to chloramphenicol and cipro-floxacin (MIC=50μg/ml). Compounds **3c** showed equipotential activity to ampicillin (MIC=250μg/ml) while compounds **3a**, **3d** found to possess comparable activity to ampicillin (MIC=250μg/ml) and modest to chloramphenicol and ciprofloxacin (MIC=50μg/ml) against *Staphylococcus aureus* organism. In case of inhibiting *Streptococcus pyogenes*, compounds **3c** (MIC=100μg/ml) exhibited inhibitory effect as same as ampicillin (MIC=100 μg/ml) and less effective than chloramphenicol and ciprofloxacin (MIC=50μg/ml) whereas compounds **3b**, **3e** (MIC=125 μg/ml)exerted significant potential to ampicillin (MIC=100 μg/ml) and less potential to chloramphenicol and ciprofloxacin (MIC=50μg/ml) against *Streptococcus pyogenes*.

In case of inhibition of Gram-negative bacteria, compound **3d** (MIC=62.5μg/ml) demonstrated excellent activity compared to ampicillin (MIC=100 μg/ml) while compound **3b** (MIC=100μg/ml) showed equipotent activity to ampicillin (MIC=100μg/ml) and less potential to chloramphenicol (MIC=50μg/ml) and ciprofloxacin (MIC=25μg/ml) against *Escherichia coli*.

The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and were found less effective than the employed standard drugs. The antibacterial results revealed that most of the prepared compounds showed improved activity against the Gram-negative bacteria rather than Gram-positive bacteria.

4. CONCLUSION

All the structures were in good agreement with spectral as well as physical data. From the mentioned results in Table 1, it was found that the highest activity obtained with compound 3c. This clearly indicates that amine group is essential for good activity all other derivatives indicate moderate activity against gram positive and gram negative bacteria.

Table 1: *In vitro* antimicrobial activity of the synthesized compounds [3a-3g]

Entry	Antimicrobial activity(MIC) µg/ml			
	Antibacterial activity			
	Gram positive Bacteria		Gram negative Bacteria	
	S.*aureus*	S.*pyogenes*	E.*coli*	P.*aerug*
3a	500	200	250	250
3b	100	100	100	200
3c	100	100	125	125
3d	250	250	62.5	250
3e	500	125	250	125
3f	250	250	62.5	250
3g	500	125	250	125
Ampiciliin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25

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