SYNTHESIS AND CHARACTERIZATION OF SOME QUINOXALINE DERIVATIVES AND THE STUDY OF BIOLOGICAL ACTIVITIES

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ABSTRACT

In continuation of our endeavor towards the development of potent and effective anticancer and antimicrobial agents. A certain Quinoxaline derivatives have been prepared, which have several pharmaceutical applications. Quinoxaline derivatives are benzoheterocycles, quinoxaline-2, 3-diones. Some of quinoxaline compounds are synthesized and characterized such as 6,7-dichloroquinoxaline-2,3-dione and 6,7-dimethylquinoxaline-2,3-dione . Biological activity results were satisfactory.

Keywords : Quinoxaline derivatives, Organic synthesis and Biological activity.

1. INTRODUCTION

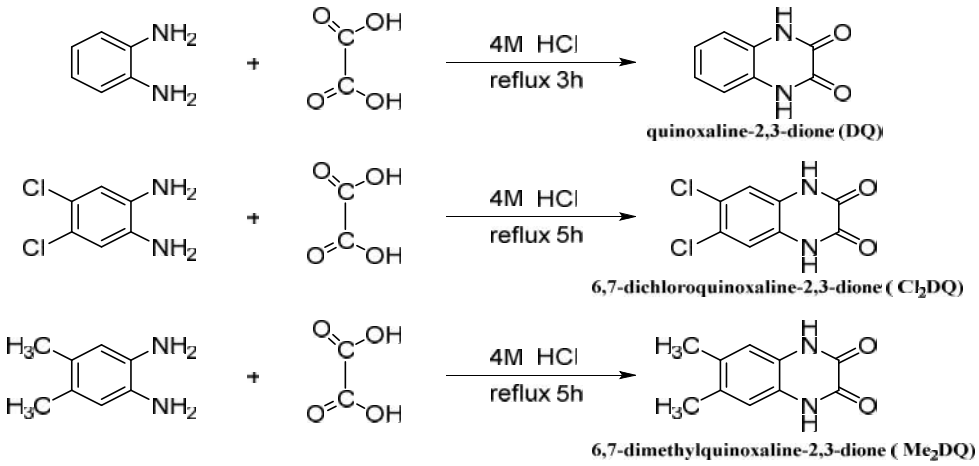
Quinoxaline and its derivatives are an important class of benzoheterocycles [1-4] displaying a broad spectrum of biological activities [5-8] which have made them privileged structures in combinatorial drug discovery libraries [9-14]. They have also found to have other applications such as dyes [15-17] and building blocks in the synthesis of organic semiconductors [18,19], and they also serve as useful rigid subunits in macro cyclic receptors or molecular recognition [20,21] and chemically controllable switches [22].Accordingly, we need to design new compounds having anticancer and antimicrobial activity at the same time. Quinoxaline derivatives display a broad spectrum of biological activities including antimicrobial [23–25], and they constitute useful intermediates in organic synthesis and medicinal chemistry [26–29]. In addition, quinoxaline moiety constitutes part of the chemical structure of various antibiotics such as echinomycin, levomycin

and actinoleutin that are known to inhibit the growth of Gram positive bacteria [30]. Outside medicine quinoxaline derivatives also have been found to have applications in efficient electron luminescent materials [31], chemically controllable switches [32]. Many researchers have reported the synthesis and biological activity of quinoxaline derivatives [33–36]. In the light of these facts it has been decided to synthesize some new quinoxaline derivatives in the hope of obtaining better antimicrobial agents. All the synthesized compounds were screened for their antimicrobial activity.

2. EXPERIMENTAL

Orthophnylenediamine, oxalic acid dihydrate ($C_2H_2O_4.2H_2O$), 4,5-dichloro-1,2-phenylene diamine ($C_6H_6N_2Cl_2$) and 4,5-dimethyl-1,2-phenylenediamine ($C_8H_{12}N_2$) were used as purchased from Sigma–Aldrich Chemical Co. Inc. All solvents were of analytical reagent grade and purified according to the standard methods [37]. The following compounds were synthesized according to the **scheme 1** given below. Elemental analyses were performed using a Perkin–Elmer 2400 CHN elemental analyzer. ^{1}H NMR spectra were performed on a JEOL- 270 MHz, NMR spectrometer in DMSO-d_6 solvent and TMS was used as an internal reference. Infrared spectra (4000–400 cm^{-1}) were recorded as KBr pellets on a Unicam Mattson 1000 FTIR spectrometer. The electronic absorption spectra were recorded by using Unicam UV2–300 UV–Vis spectrometer. Samples of $2.6x10^{-4}$ mol dm^{-3} concentrations in DMSO were measured against the solvent in the reference cell. Antimicrobial activity of the tested samples for the

compounds was determined using a modified Kirby- Bauer disc diffusion method [23].



Scheme 1: Synthesizes of the quinoxaline derivatives compounds

2.1. SYNTHSIS

2.1.1. Synthesis of the quinoxaline-2,3-dione (DQ).

O-phenylenediamine (5.4 g, 5 mmol) and oxalic acid (6.3 g, 5 mmol) in presence of 4.0 M HCl (50 ml) were heated together under reflux for three hours with stirring. After cooling , the solid product was filtered and washed with water. 2,3-dihydroxyquinoxaline was thus obtained as grey-colored crystals with m.p. higher than 300˚C .Quinoxaline-2,3-dione (DQ) ligand was synthesized according to the reported literature [39].

2.1.2. Synthesis of the 6,7-dichloroquinoxaline-2,3-dione (Cl2DQ)

4,5-dichloro-1,2-phenylenediamine (1.54 g, 10 mmol) and oxalic acid (1.26 g, 10 mmol) in presence of 4.0 M HCl (50 ml) were heated together

under reflux for five hours with stirring. After cooling , the solid product was filtered and washed with water. 6,7-dichloroquinoxaline-2,3-diol was thus obtained as brown- colored crystals with milting point higher than 300 ˚C . (Yield 72 %).

2.1.3. Synthesis of the 6,7-dimethyl quinoxaline-2,3-dione (Me2DQ)

4,5-dimethyl-1,2-phenylenediamine (1.54 g, 10 mmol) and oxalic acid (1.26 g, 10 mmol) in presence of 4.0 M HCl (50 ml) were heated together under reflux for five hours with stirring. After cooling , the solid product was filtered and washed with water. 6,7-dimethylquinoxaline-2,3-diol was thus obtained as brown- colored crystals with milting point higher than 300 ˚C . (Yield 79 %).

3. RESULTS AND DISCUSSION

3.1. Characterization of the quinoxaline-2,3-dione (DQ).

Elemental analysis (M.Wt. 162, Found: C 58·98, H 3·75, N 17·30% Calcd.: C 59·26, H 3·73, N 17·28%) indicated that has the molecular formula $C_8H_6N_2O_2$. The infrared spectrum shows sharp bands at ~3150, 1712, 1480, and 1400 cm^{-1} which can be assigned to m(NH), m(C=O), and m(CN)amide, and d(NH), respectively [39,40]. This spectral behavior is in good agreement with the solid-state structure of the compound. The ^1H NMR spectrum was recorded in DMSO-d_6. As shown one doublet at δ7.05 ppm with four protons assigned to the aromatic protons and one singlet at 11.87 ppm with two protons assigned to the NH group. The electronic absorption spectrum in DMSO solvent . The spectrum of free ligand revealed

two absorptions at 300 and 400 nm attributable to the intraligand, π–π* and n-π* transitions.

3.2. Characterization of the 6,7-dichloroquinoxaline-2,3-dione (Cl_2DQ)

Elemental analysis (M.Wt. 231.04, Found: C 42.59; H 2.17; N 12.17; Cl 30.05% Calc. : C 41.59;H 1.75 ;N 12.13 ;Cl 30.69%) indicated that has the molecular formula $C_8H_4N_2O_2Cl_2$. The infrared spectrum recorded on solid sample in KBr, revealed characteristic vibrational bands due to the stretching vibrations of N-H and C=O groups. These bands were observed at 3416 and 1728 cm-1; respectively. Vibrational bands attributed to the C-H stretches were observed at 3060 and 3042 cm-1. These results may suggest that exists in the keto-form. The ^{1}HNMR spectrum has been in DMSO-d_6 solvent displayed signal at 7.23 ppm due to the protons of the phenyl ring of the quinoxaline moiety. In addition a singlet attributable to N-H protons were observed at 11.9 ppm. The electronic absorption spectrum in DMSO solvent . The spectrum of free ligand revealed two absorptions at 324 and 410 nm attributable to the intraligand, π–π* and n-π* transitions.

3.3. 6,7-dimethyl quinoxaline-2,3-dione (Me_2DQ)

Elemental analysis (M.Wt. 190.20, Found: C 63.70; H 6.17; N 16.32%; Calc. : C 63.15; H 5.30; N 14.73%) indicated that has the molecular formula $C_{10}H_{10}N_2O_4$. The IR spectrum revealed vibrational bands at 3445 and 3325 cm^{-1} due to asymmetric and symmetric by vibrations of the N–H groups. Stretching vibration of the C-H stretches of the phenylne group of the quinoxaline moiety were observed at 3071 and 3050 cm^{-1}. Additional vibrational frequencies corresponding to C-H stretches of the methyl groups

were observed at 2944 and 2862cm^{-1}. The ^{1}HNMR spectrum in DMSO-d^{6} displayed a signal at 6.82 ppm corresponding to the two protons of the phenyl ring in quinoxaline moiety. Also the spectrum displayed signal due to the methyl protons at 3.65 ppm. The OH proton are identified at 11.76 δ as a singlet. The electronic absorption spectrum in DMSO solvent. The spectrum revealed two absorptions at 350 and 445 nm attributable to the intraligand, π–π* and n-π* transitions.

3.4. Antimicrobial Activities of compounds

Understanding the role of chemical structure on influencing biological activity is very important. Studies on the structure activity relationship have shown the importance of the lipophilic nature of biologically active molecules [41,42]. Biological importance of quinoxaline is well known as mentioned earlier under the review of literature. This prompted us to synthesize quinoxaline derivatives. The antimicrobial activity of the three compounds were tested by the disc diffusion method against two types of pathogenic bacteria, namely, S. aureus and E. Coli by using DMSO as a solvent and tetracycline as a control. Also, the antifungal activity for the free ligand and the complex were tested against A. flavus and C. albicans fungi using Amphotericin as a control. The inhibition zone diameters for the antimicrobial activity were measured and the results are presented in **Table I**. The results indicate that the compounds show biological activities against both bacteria and fungi. Although the inhibition zone diameters are lower than tetracycline and Amphotericin B standards.

TABLE I. ANTIMICROBIAL ACTIVITIES OF THE COMPOUNDS

Sample	Inhibition zone diameter (mm/mg sample)			
	Escherichia Coli (gram-negative)	Staphylococcus aureus (gram-positive)	Aspergillus Flavus	Candida Albicans
DMSO[a]	0.0	0.0	0.0	0.0
Tetracycline [b]	31	33	-	-
Amphotericin B[c]	-	-	17	21
Quinoxaline-2,3-dione (DQ).	18	17	9	13
6,7-dichloroquinoxaline-2,3-dione (Cl_2DQ)	15	16	12	12
6,7-dimethyl quinoxaline-2,3-dione (Me_2DQ)	21	19	0.0	14

[a] DMSO solvent was used as negative control.
[b] Standard antibacterial agent.
[c] Standard antifungal agent.

4. CONCLUSION

Quinoxaline and its derivatives have biological importance as it is reported by many researchers. However, it is believed that those compounds can be anti-cancer activities appear to be associated with some metals such as ruthenium, which is worth trying [43].

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