IJPSR (2014), Vol. 5, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 October, 2013; received in revised form, 16 February, 2014; accepted, 03 May, 2014; published 01 June, 2014

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF Cu(II), Co(III) AND Fe(III) COMPLEXES OF 2-BENZOYL-3-(NITROPHENYL)QUINOXALINE

S. Jone Kirubavathy [1], R. Velmurugan [1], K. Parameswari [2] and S. Chitra*[2]

Department of Chemistry, Kongunadu Arts and Science College [1], Coimbatore-641 029, Tamil Nadu, India
Department of Chemistry, P. S.G. R. Krishnammal College for Women [2], Coimbatore- 641 004, Tamil Nadu, India

Keywords:

Square planar geometry, Cu(II) complex, Co(III) complex, Fe(III) complex, Antimicrobial activity, spectral studies

Correspondence to Author:

S. Chitra

Department of Chemistry, P. S.G. R. Krishnammal College for Women, Coimbatore- 641 004, Tamil Nadu, India

E-mail: chitrapsgrkc@gmail.com

ABSTRACT: A new series of transition metal complexes of the type ML where M = Cu(II), Co(III) and Fe(III) and L = 2-benzoyl-3-(nitrophenyl)quinoxaline have been characterized and the structural features were arrived from the elemental analysis, magnetic susceptibility, molar conductance, FT- IR, UV-Vis and NMR spectral data. From the spectral measurements and magnetic susceptibility values a square planar geometry was proposed for Cu(II) complex and an octahedral geometry for Co(III) and Fe(III) complexes. The qualitative and quantitative antimicrobial activity test results proved that all the prepared complexes are very active especially against *E. coli*, *S. aureus*, *C. albicans* and *A. niger*.

INTRODUCTION: Heterocyclic compounds represent an important class of biologically active molecules especially those containing quinoxaline derivatives have evoked considerable attention in recent years as these are endowed. Quinoxalines are a versatile class of nitrogen containing heterocyclic compounds and they constitute useful intermediates in organic synthesis. `Quinoxaline, also called a benzopyrazine, in organic chemistry, is a heterocyclic compound containing a ring complex made up of a benzene ring and a pyrazine ring and they are isomeric with cinnolenes, phthalazines and quinazolines.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(6).2498-07

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(6).2498-04

There are a number of processes available to generate quinoxaline but generally, they are synthesized by the condensation of 1, 2-dicarbonyls with 1, 2-diamines in presence of suitable catalyst using various solvent systems. They have been widely used in dyes, pharmaceuticals [1, 2] and electrical/photochemical materials [3-7].

Quinoxaline ring moiety constitute part of the chemical structures of various antibiotics such as *Echinomycin, Levomycin and Actinoleutin* [8-11] that are known to inhibit growth of gram positive bacteria and are active against various transplantable tumors.

They possess well known biological activities including AMPA/GlyN receptor antagonist [12], antihistaminic agents [13], anti-trypanosomal activity [14], anti-herps [15], antiplasmodial activity [16], Ca uptake/ Release inhibitor [17], inhibit vascular smooth muscle cell proliferation [18-20].

The complexes of these bioactive quinoxalines are not found much in literature and the aim of the present work is to synthesize these bioactive quinoxaline derivative and their metal complexes and screen for their antimicrobial activity against several bacterial and fungal strains.

MATERIALS AND METHODS:

All reagents, 1, 2-diketone, o-phenylene diamine and metal chlorides were purchased from Sigma Aldrich, India.

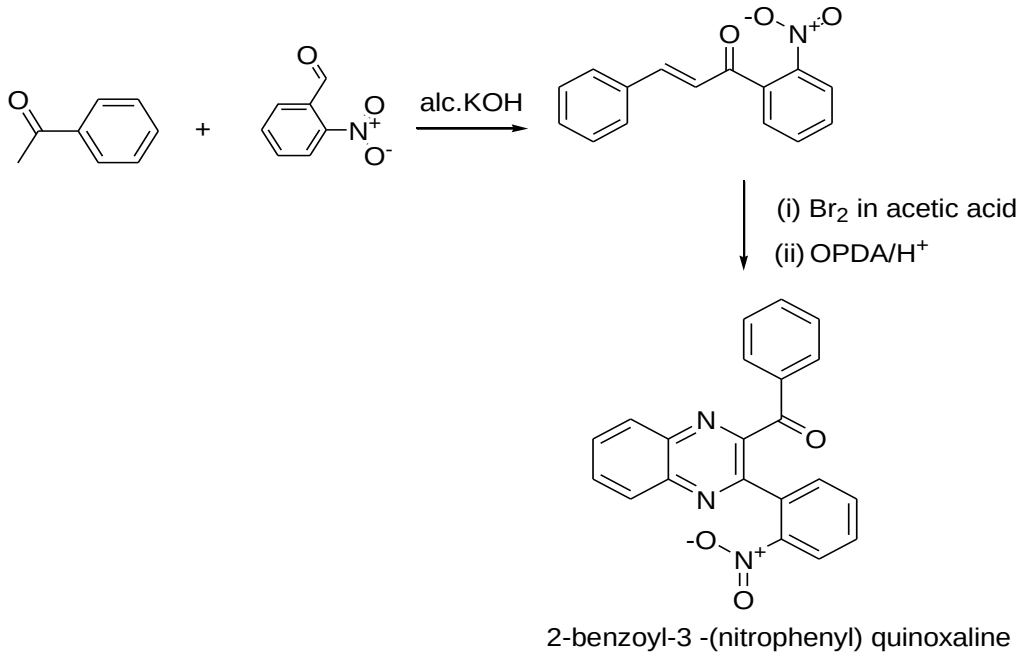
Physical Measurements: Microanalytical data of the compounds were recorded in the *Elementar Vario EL III* CHN Analyzer. The FT-IR spectra of the samples were recorded on a *Shimadzu* spectrophotometer in 4000-400 cm^{-1}. The UV-Visible spectra were recorded on an *Elico SL 159* UV-Vis Spectrophotometer. The X band ESR spectra of the copper complex was recorded at 77K on a *JES-FA200* ESR spectrophotometer using diphenylpicrylhydrazyl(DPPH) as internal standard. Magnetic susceptibility measurements of the complexes were carried out by *Guoy balance* using copper sulphate as the calibrant. The molar conductance of the complexes was measured using a *systronics* conductivity bridge at room temperature in DMSO solution. The antimicrobial activities of the ligand and its complexes were carried out by disc diffusion method.

Preparation of 2-benzoyl-3-(nitrophenyl) quinoxaline ($C_{21}H_{15}N_3O_2$):

Synthesis of 3-(2-Nitro-phenyl)-1-phenyl-propenone: An equimolar amount of acetophenone (1.20ml, 0.01mmol) and o-nitrobenzaldehyde (1.52g, 0.01 mmol) were mixed and stirred for 30 minutes. The contents were cooled and 15ml aq. KOH was added slowly and the mixture was stirred for 3 hours. The solid obtained was filtered, washed, dried and recrystallised from ethanol.

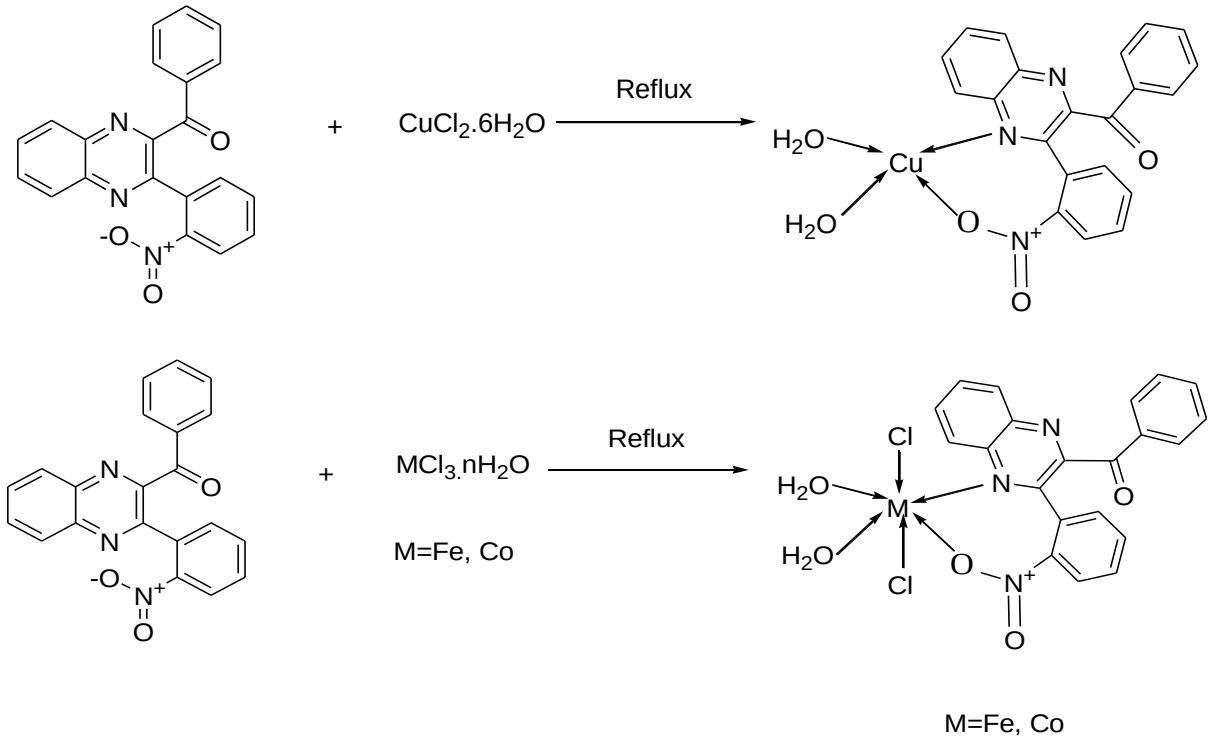
Synthesis of bromo derivative of 3-(2-Nitro-phenyl)-1-phenyl-propenone: In continuation of above reaction the product were dissolved in 30ml of acetic acid and added 2ml of bromine. The mixture was stirred for 30 minutes; the product obtained was filtered, dried and recrystallized from ethanol.

Synthesis of 2-benzoyl-3-nitrophenyl quinoxaline: The quinoxaline derivative was prepared by refluxing a mixture of o-phenylene diamine and the bromo derivative in methanol (1:1) in the presence of conc. H_2SO_4 (2 drops) for 30 minutes. The product obtained was filtered, dried and recrystallized from ethanol [21].



SCHEME 1: SYNTHESIS OF 2-BENZOYL-3-(NITROPHENYL) QUINOXALINE

Synthesis of complexes: The alcoholic solution of the ligand and metal chlorides were refluxed for 5 hours. The solid obtained was collected, filtered, washed with water and dried.



SCHEME 2: SYNTHESIS OF COMPLEXES

Metal estimation: Metal estimation for Cu(II), Co(III) and Fe(III) complexes was done by incineration method. The metal complexes were taken in a silica crucible. Ammonium oxalate was added to it and it was incinerated 3-4 hours with Bunsen flame till corresponding stable metal oxide was formed. It was cooled and weighed again till constant values were obtained. From the weight of the metal oxides, the compositions of metal in the complexes were calculated**.**

Antimicrobial studies: The antibacterial activity of the ligand and the metal complexes were screened for gram positive bacteria and gram negative bacteria namely *S. aureus, E. coli*, respectively by the disc diffusion method using agar nutrient as the medium. The antifungal activities were screened for the organisms *A. niger* and *C. albicans* by the disc diffusion method cultured on potato dextrose agar as medium. The plate was incubated 24 hours for bacteria and 72 hours for fungi. During this period, the test solution diffused and the growth of the inoculated microorganisms was affected. The inhibition zone was developed, at which the concentration was noted [22, 23].

Anticancer activity:

Determination of anticancer activity of $Co(C_{21}H_{15}N_3O_2)Cl_3(H_2O)_2$ complex: The human cervical cancer cell line (HeLa) was obtained from National Centre for Cell Science (NCCS), Pune and grown in Eagles Minimum Essential Medium (EMEM) containing 10% fetal bovine serum (FBS). All cells were maintained at 37°C, 5% CO_2, 95% air and 100% relative humidity. Maintenance cultures were passaged weekly, and the culture medium was changed twice a week.

Cell Treatment Procedure: The monolayer cells were detached with trypsin-ethylenediamine tetraacetic acid (EDTA) to make single cell suspensions and viable cells were counted using a hemocytometer and diluted with medium containing 5% FBS to give final density of $1x10^5$ cells/ml. one hundred microlitres per well of cell suspension were seeded into 96-well plates at plating density of 10,000 cells/well and incubated to allow for cell attachment at 37°C, 5% CO_2, 95% air and 100% relative humidity. After 24 hours the cells were treated with serial concentrations of the test samples.

They were initially dissolved in neat dimethylsulfoxide (DMSO) and diluted to twice the desired final maximum test concentration with serum free medium. Additional four, 2 fold serial dilutions were made to provide a total of five sample concentrations. Aliquots of 100 µl of these different sample dilutions were added to the appropriate wells already containing 100 µl of medium, resulted the required final sample concentrations. Following drug addition, the plates were incubated for an additional 48 hours at 37°C, 5% CO_2, 95% air and 100% relative humidity. The medium containing without samples were served as control and triplicate was maintained for all concentrations.

MTT Assay: 3-[4,5-dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide (MTT) is a yellow water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. Therefore, the amount of formazan produced is directly proportional to the number of viable cells.

After 48 hours of incubation, 15µl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37°C for 4hours. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100µl of DMSO and then measured the absorbance at 570 nm using micro plate reader. The % cell inhibition was determined using the following formula;

% cell Inhibition = 100- Abs (sample)/Abs (control) x 100

Nonlinear regression graph was plotted between % Cell inhibition and Log_{10} concentration and IC_{50} was determined using Graph Pad Prism software [36, 37].

RESULTS AND DISCUSSION:

General properties: The analytical data of the complexes are given in **table 1**.

TABLE 1: PHYSICAL, CHARACTERIZATION, ANALYTICAL AND MAGNETIC SUSCEPTIBILITY DATA OF THE COMPLEXES

Compound	Mol. Wt	Color	Yield	% Found (Calculated)				μ_{eff} (BM)
				M	C	H	N	
$C_{21}H_{15}N_3O_2$	341.32	Yellowish brown	80	-	74.01 (73.89)	4.58 (4.42)	12.86 (12.31)	-
$Cu(C_{21}H_{15}N_3O_2)Cl(H_2O)$	458.61	Green	62	8.29 (8.51)	67.36 (67.54)	4.17 (4.02)	11.91 (11.25)	1.96
$Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$	507.16	Brown	68	7.63 (7.41)	63.44 (63.39)	4.03 (4.02)	10.96 (10.56)	4.14
$Fe(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$	504.11	Brown	60	7.41 (7.06)	63.73 (63.64)	4.07 (4.04)	10.69 (10.60)	5.81

The complexes are soluble in common polar solvents but readily soluble in DMF and DMSO to give stable solutions at room temperature. In the solid state, the Cu(II), Co(III) and Fe(III) complexes are stable in air allowing physical measurements. The molar conductance of the complexes is negligible showing their non-electrolytic nature [24]. The analytical data of the ligand and the complexes is in good agreement with the experimental values and the molecular formula for the complexes are $Cu(C_{21}H_{15}N_3O_2)Cl(H_2O)$, $Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$ and $Fe(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$.

NMR Spectrum of the ligand: The NMR spectrum (**Fig. 1**) of the ligand shows two sets of multiplets around δ 7.47 - 7.75 ppm and δ 8.15-8.21 ppm due to the phenyl and the benzoyl ring attached to the second and the third position of the quinoxaline ring and protons of the quinoxaline ring respectively.

The above δ values confirm the structure of the ligand 2-benzoyl-3-(nitrophenyl) quinoxaline.

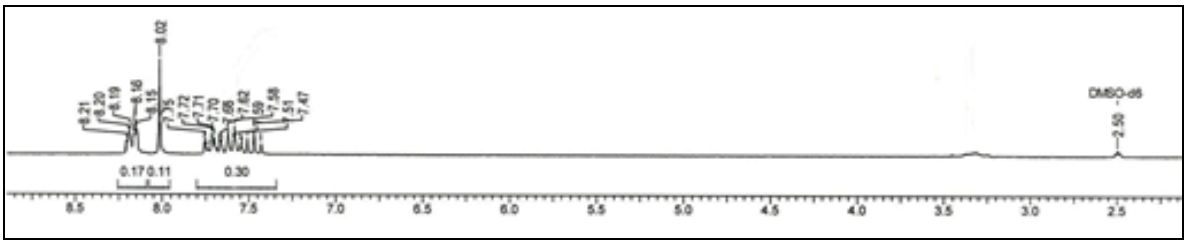


FIGURE 1: NMR SPECTRUM OF LIGAND

FT-IR Spectral data of the Complexes: The spectra of the complexes illustrate broad band at 3300 cm^{-1} is due to the presence of water molecule. The C = N stretching band in the free ligand is found to be at 1606 cm^{-1}. This is shifted to lower wave number 1571, 1580 and 1579 cm^{-1} in Cu(II), Co(III) and Fe(III) complexes respectively indicating the participation of the azomethine nitrogen of the quinoxaline ring in coordination. New bands observed at 542, 605 and 590 cm^{-1} in Cu(II), Co(III) and Fe(III) complexes which are not seen in the spectrum of the ligand can be attributed to M-N stretching vibration. From the IR spectra, it is proved that the coordinating site is 'N' in the quinoxaline ring [25, 26]. The N-O stretching frequency of the nitro group is observed at 1394 cm^{-1} for the ligand and for the complexes it is shifted to lower frequencies ie 1375, 1375, 1370 cm^{-1} for Cu(II), Co(III) and Fe(III) complexes respectively. This proves that the 'O' in the nitro group is coordinated forming a seven membered chelate ring in the complexes [27, 28]. The IR spectra of ligand and the complexes are shown in **Fig. 2-5** and the values are tabulated in **table 2**.

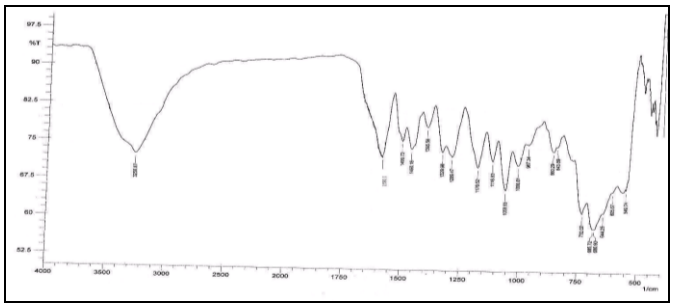


FIGURE 2. IR SPECTRUM OF LIGAND

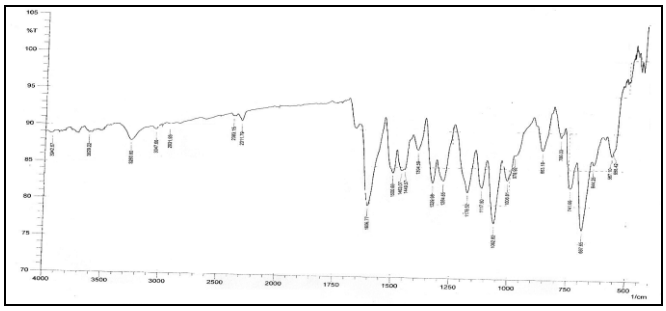


FIGURE 3: IR SPECTRUM OF Cu(II) COMPLEX

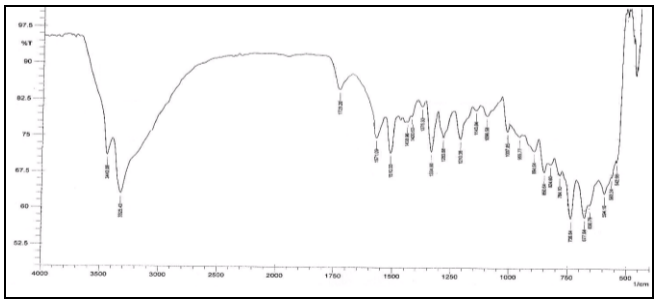


FIGURE 4: IR SPECTRUM OF Co(III) COMPLEX

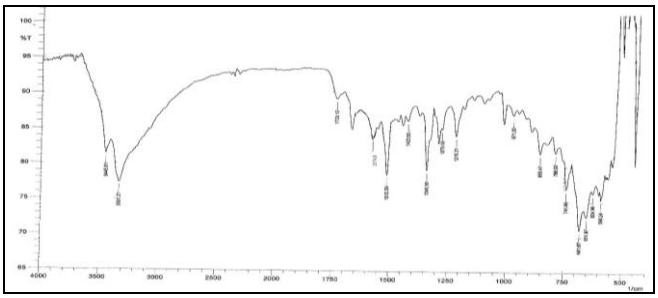


FIGURE 5: IR SPECTRUM OF Fe(III) COMPLEX

TABLE 2: IR STRETCHING FREQUENCIES 2-BENZOYL-3-(NITROPHENYL)QUINOXALINE AND ITS COMPLEXES IN Cm^{-1}

Complex	γ (C=N)	γ (H_2O)	γ (M-N)	γ (N-O)
Ligand	1606	-	-	1394
$Cu(C_{21}H_{15}N_3O_2)Cl(H_2O)$	1571	3325	542	1375
$Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$	1580	3258	605	1375
$Fe(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$	1579	3331	590	1370

Electronic Spectra of the complexes: The electronic spectral data is in relevance with proposed geometry of complexes and it is shown in **table 3**. The electronic absorption spectrum of $Cu(C_{21}H_{15}N_3O_2)Cl(H_2O)$ shows band at 324 and 450 nm. These corresponds to intra ligand charge transfer bands and the transition at 450 nm corresponds to $^2B_{1g} \rightarrow ^2B_{2g}$. These electronic transitions and observed 1.96 BM magnetic moment value suggests square planar geometry around Cu(II). $Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$ complex shows band at 297 and 451 nm. The first transition is the intra ligand charge transfer transitions and the transition at 451 nm is due to $^6A_{1g} \rightarrow ^1B_{1g}$ transition which corresponds to octahedral geometry around cobalt metal ion. The electronic absorption spectra of $Fe(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$ show weak bands at 324 and 595 nm. The band at 595 nm corresponds to $^6A_{1g} \rightarrow ^4T_{1g}$ transition and the other transitions are due to the INCT transitions. Electronic transitions together with the magnetic moment value 5.81 BM suggests high spin octahedral geometry for Fe(III) complex [29-30]. The proposed geometry of the complexes is shown in **Fig. 6**.

TABLE 3: ELECTRONIC ABSORPTION SPECTRAL DATA OF THE COMPOUNDS:

Compound	Solvent	Absorption (in nm)	Band Assignment	Geometry
$C_{21}H_{15}N_3O_2$	DMF	312	π-π*	-
$Cu(C_{21}H_{15}N_3O_2)Cl(H_2O)$	DMF	324 450	INCT $^2B_{1g} \rightarrow ^2B_{2g}$	Square Planar
$Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$	DMF	324 595	INCT $^6A_{1g} \rightarrow ^1B_{1g}$	Octahedral
$Fe(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$	DMF	297 451	INCT $^6A_{1g} \rightarrow ^4T_{1g}$	Octahedral

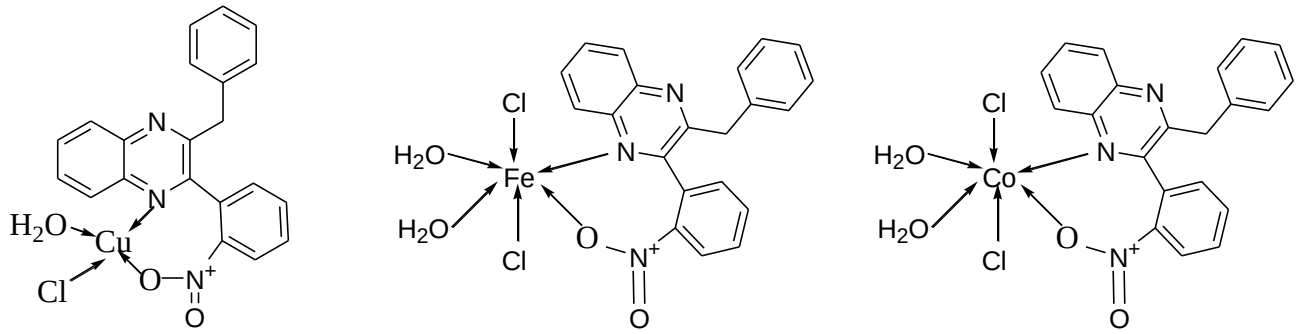


FIGURE 6: PROPOSED GEOMETRY OF $[Cu(C_{21}H_{15}N_3O_2)(H_2O)Cl]$, $[Fe(C_{21}H_{15}N_3O_2)(H_2O)_2Cl_2]$ AND $[Co(C_{21}H_{15}N_3O_2)(H_2O)_2Cl_2]$ COMPLEXES

Molecular modeling: The possible geometries of metal complexes were evaluated using the molecular calculations with Argus lab 4.0.1 version software. The metal complexes were built and geometry optimization was done using this software. The molecular modeling pictures of the metal complexes are shown in **Fig. 7**.

Antimicrobial activity: The antimicrobial studies of the ligand and their complexes were studied against two fungi (*C. albicans, A. niger*) and two bacteria (*E. coli, S. aureus*) in three different concentrations and it is tabulated in **Table 4 and 5**. Cobalt (III) complexes have very good activity more than the standard against the fungal strains and the Fe(III) complexes have very good activity against the bacterial strains. All the other complexes are comparatively good. The zone of inhibition for antifungal activity is shown in **Fig. 8** and for antibacterial activity in **Fig. 9**. When the activity of the ligand and the complexes are compared, the complexes have more activity than the ligand. A comparative study of the ligand and their complexes indicate that the metal complexes exhibited higher antimicrobial activity than the free ligand in most of the case. Such increased activity of the complexes can be explained with respect to Overtone's concept and Tweedy's chelation theory.

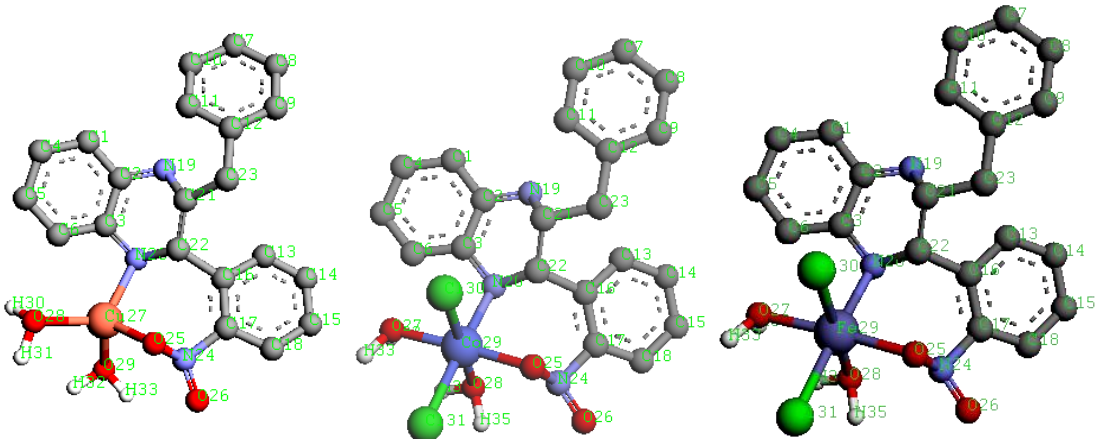


FIGURE 7: MOLECULAR MODELING PICTURES OF THE METAL COMPLEXES

TABLE 4: SCREENING FOR ANTIFUNGAL ACTIVITY OF $C_{21}H_{15}N_3O_2$ AND ITS COMPLEXES

S. No.	Organisms	Zone of Inhibition (mm)				
		Standard	Ligand	Cu(II)	Co(III)	Fe(III)
1	*A. Niger*	11	10	10	20	10
2	*C. Albicans*	13	12	14	19	10

TABLE 5: SCREENING FOR ANTIBACTERIAL ACTIVITY OF $C_{21}H_{15}N_3O_2$ AND ITS COMPLEXES

S. No.	Organisms	Zone of Inhibition (mm)				
		standard	Ligand	Cu(II)	Co(III)	Fe(III)
1	*S. Aureus*	11	09	15	13	17
2	*E. Coli*	16	13	17	15	13

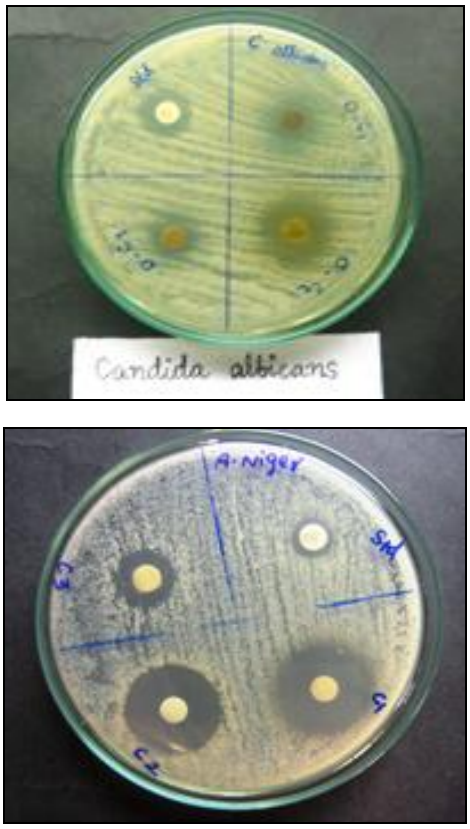


FIGURE 8: ZONE OF INHIBITION FOR ANTIFUNGAL ACTIVITY

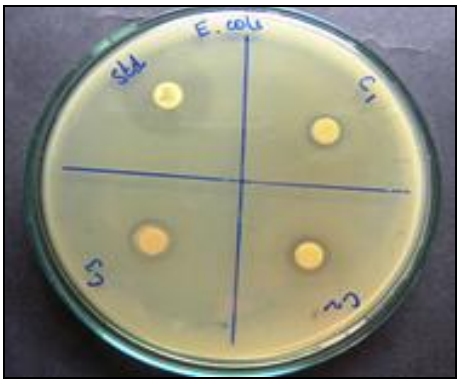


FIGURE 9: ZONE OF INHIBITION FOR ANTI-BACTERIAL ACTIVITY

According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only the lipid soluble materials whose liposolubility is an important factor, which controls the antimicrobial activity. On chelation, the polarity of the metal ion is reduced to a great extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of pi electrons over the whole chelate ring and enhances the lipophilicity of the complexes.

This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organisms [31-34]. It is evident from **table 6 and 7** that the MIC value for $Fe(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$ against *S. aureus* and *E. coli* is 250 µg/ml and 500 µg/ml respectively and the MIC value for $Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$ against *C. albicans* and *A. niger* is 125 µg/ml.

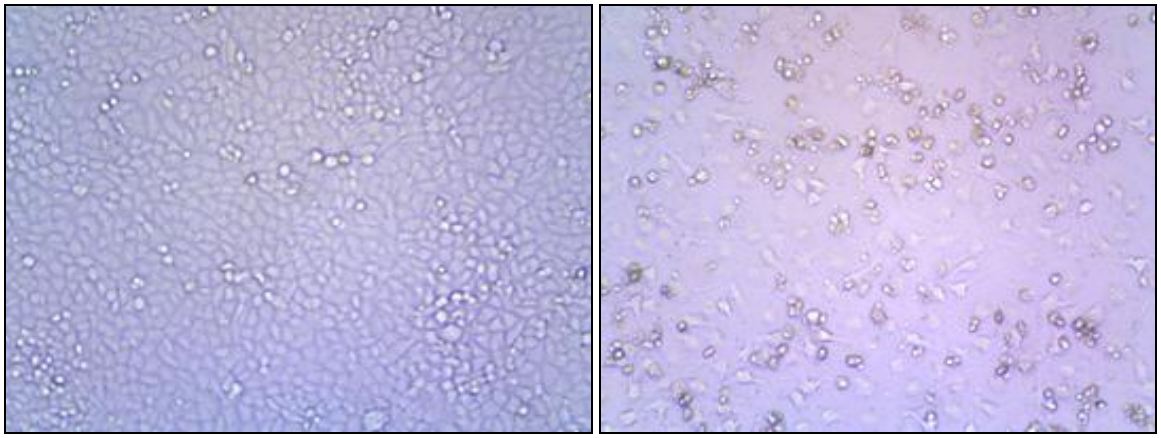
TABLE 6: MIC VALUE OF $Fe(C_{23}H_{18}N_2)_2Cl_3(H_2O)$ COMPLEX IN ANTIBACTERIAL ACTIVITY

S. No.	Organisms	500 µg/ml	250 µg/ml	125 µg/ml	62.5 µg/ml	31.25 µg/ml	15.625 µg/ml	7.812 µg/ml
1.	*S. aureus*	-	-	+	+	+	+	+
2.	*E. coli*	-	+	+	+	+	+	+

TABLE 7: MIC VALUE OF $Co(C_{23}H_{18}N_2)_2Cl_3(H_2O)$ COMPLEX IN ANTIFUNGAL ACTIVITY

S. No.	Organisms	500 µg/ml	250 µg/ml	125 µg/ml	62.5 µg/ml	31.25 µg/ml	15.625 µg/ml	7.812 µg/ml
1.	*C. Albicans*	-	-	-	+	+	+	+
2.	*A. Niger*	-	-	-	+	+	+	+

Anticancer activity of $Co(C_{21}H_{15}N_3O_2)Cl_2(H_2O)_2$ complex: To verify this bio-reductive activation mechanism under in-vitro conditions, cytotoxicity studies were carried out. Moreover, as the balance between the therapeutic potential and toxic side effects of a compound is very important when evaluating its usefulness as a pharmacological drug, experiments were designed to investigate the *in-vitro* cytotoxicity of the synthesized cobalt complex against the human breast cancer cell line MCF 7. Cytotoxicity was determined by means of a colorimetric micro culture MTT assay, which measures mitochondrial dehydrogenase activity as an indication of cell viability. It is evident that the number of cells decreased with an increase in the concentration of the Co(III) complex (**Fig. 10**).



a) 0.05 µM Concentration **b) 50 µM Concentration**

FIGURE 10: ANTICANCER ACTIVITY FOR CO(III) COMPLEX

The complex showed higher potential antineoplastic activity which is evidenced by low IC_{50} values (50% inhibitory concentration after exposure for 48 hours in MTT assay) of 55.69µg/ml which is about twice resistant as CDDP (35.0 µM) against the cancer cells throughout the duration of the experiment [35].

CONCLUSION: The heterocyclic compound 2-benzyl-3-(nitrophenyl) quinoxaline coordinates to the Cu(II), Co(III) and Fe(III) ions using the nitrogen in the quinoxaline ring and the oxygen of the nitro substituent. The assignment of the square planar for Cu(II) and the octahedral geometry for Co(III) and Fe(III) complexes with seven membered chelate ring is corroborated by magnetic, infrared and electronic spectral measurements. The *in-vitro* anti-microbial studies show that the Cu(II) and the Fe(III) complex has a broad spectrum antibacterial activities against *E.*

coli and *S. aureus* and the Co(III) complex antifungal activities against *C. albicans* and *A. niger*. The *in-vitro* cytotoxicity study show that the Co(III) complex exhibits *in-vitro* anti-tumour activity against the human breast cancer cells with IC_{50} 55.69 μM.

In conclusion, new classes of quinoxaline heterocycles were synthesized and the results revealed that the compounds possess significant antimicrobial and anticancer activity. Therefore, this study would be a fruitful matrix for the development of novel class of quinoxaline derivatives as interesting lead molecules for further synthetic and biological evaluation.

REFERENCES:

1. Gazit A., App H., McMahon G., Chen J., Levitzki A., Bohmer F. D., Tyrphostins.5. Potent inhibitors of platelet-derived growth factor receptor tyrokinase: structure-activity relationships in quinoxalines, quinolines and indole synthesis, *J. Med. Chem*. 1996; 39, 2170-2177.
2. [2] Sehlstedt U., Aich P., Bergman J., Vallberg H., Norden B., Graslund A, Interactions of the antiviral quinoxaline derivative 9-OH-B220{2,3-dimethyl-6-(dimethylaminoethyl)-9hydroxy-6H-indolo-[2,3-b] quinoxaline} with duplex and triplex forms of synthetic DNA and RNA, *J. Mol. Biol.* 1998; 278,31-56.
3. Dailey S., Feast J. W., Peace R J., Sage I. C., Till S., Wood E. L, Synthesis and device characterization of side chain polymer electron transport materials for organic semiconductor applications, *J. Mater. Chem.* 2001; 11, 2238-2243.
4. Brien D. O'., Weaver M S., Lidzey D G., Bradley D D C, Use of poly(phenyl-quinoxaline) as an electron transport material in polymer light emitting diodes, *Appl. Phys. Lett*. 1996; 69, 881-883.
5. Yamamoto T, Sugiyama K, Kushida T, Inoue T, Kanbara T, Preparation of New Electron Accepting p-conjugated polyquinoxalines. Chemical and Electrochemical reduction, Electrically Conducting Properties, and Light emitting diode, 1996; *J. Am. Chem. Soc*. 118, 3930-3937.
6. Yamamoto T *et al.,* p Conjugated Donor –Acceptor Copolymers constituted of p-excessive and p- deficient Arylene Units. Optical and Electrochemical properties in relation to CT structure of the polymer, *J. Am. Chem. Soc*. 1996; 118, 10389-10399.
7. Nurulla I., Yamaguchi T., Preparation and properties of new p- conjugated polyquinoxalines with aromatic fused rings in the side chain. *Polym. Bull*., 2000; 44, 231-238.
8. Yamamoto T., Lee B L., Kokubo H., Kishida H., Hirota K., Wakabayashi T., Okaoto H., Synthesis of a new thiopene Quinoxaline CT Type Copolymer with high solubility and its basic optical property. *Macromol. Rapid Commun*., 2003; 24, 440-443.
9. Dell A., William D H., Morris H R. , Smith H R., Feeney G A., Roberts J, Structure revision of the antibiotic echinomycin in solution, *J. Am. Chem. Soc.* 1975; 97, 2497-2502.
10. Bailly C., Echepare S., Gago F., Waring M. Recognition elements that determine affinity and sequence-specific binding to DNA of 2QN, a biosynthetic bis-quinoline analogue of echinomycin. *Anti-Cancer Drug Des*. 1999; 15, 291-303.
11. Eicher T., Hauptmann S., *The Chemistry of Heterocycles*; Thieme: New York, 417 (1995).
12. Nikam SS., Cordon JJ., Ortwine DJ, Design and synthesis of novel quinoxaline-2,3-dione AMPA/GlyN receptor antagonist. *J. Med. Chem.*, 1999, 42, 2266-2271.
13. Sridevi C H., Balaji K, Naidu A., Antimicrobial Evaluation and Synthesis of Some Phenylpyrazolo benzothiazoloquinoxaline Derivatives. *Journal of Chemistry*, 2010; **7**, 234-238.
14. Urquiola C., Vieites M., Aguirre G., Improving anti-trypanosomal activity of 3-aminoquinoxaline- 2-carbonitrile N1, N4-dioxide derivatives by complexation with vanadium. *Bioorg. Med. Chem.*, 2006; 14, 5503-5509.
15. Harmenberg J., Wahren B., Antiherpes virus Activity and Mechanism of Action of Indolo-(2,3-b)Quinoxaline and Analogs., *Antimicrob. Agents Chemother.*, 1988; 32, 1720-1724.
16. Zarranz B., Jaso M., Lima L M., Antiplasmodial activity of 3-trifluoromethyl-2-carbonylquinoxaline di-N-oxide derivatives. *Rev. Bras. Cienc. Farm.*, 2006; **42**, 55-67.
17. Xia H., Wang F., Yu K., Novel cyclophilin D inhibitors derived from quinoxaline exhibit highly inhibitory activity against rat mitochondrial swelling and Ca^{2+} uptake/release. *Acta Pharmacol. Sin.*, 2005, 26, 1201-1211.
18. Chung H J., Jung O J., Synthesis and biological evaluation of quinoxaline -5, 8-diones that inhibit vascular smooth muscle cell proliferation. *Bioorg. Med. Chem. Lett.*, 2005; 15, 3380-3384.
19. Bailly C., Echepare S., Gago F., Recognition elements that determine affinity and sequence-specific binding to DNA of 2QN, a biosynthetic analogue of echinomycin. *Anti-Cancer Drug Des.*, 1999; 15, 291-303.
20. Sato S., Shirator O., Katagiri K., Mode of action of quinoxaline antibiotics, Interaction of quinomycin A with deoxyribonucleic acid. *J. Antibiot.*, 1967; 20, 270-276.
21. Vekariya N A., Khunt M D., Parikh A R., Synthesis of isoxazoles and quinoxalines as potential anticancer agents. *Indian Journal of Chemistry*, 2003; 45B, 421-424.
22. Munde A S., Jagdale A N., Jadhav S M., Chondhekar T K., Synthesis, Characterization and thermal study of some transition metal complexes of an asymmetrical tetradentate Schiff base ligand, *J. Serb. Chem. Soc*. 2010; 75(3), 349-359.
23. Shelke V A., Jadhav S M., Shankarwar S G., Chondhekar T K., Synthesis, Spectroscopic investigation and antimicrobial activities of some rare earth metal complexes of biologically active asymmetrical tetradentate ligand, *Journal of chemical science and technology*, 2013; 2(2) ,61-69.
24. Geary W J. The use of conductivity measurements in organic solvents for the characterization of coordination compounds. *Co-ord. Chem. Rev.*, 1971; **7**, 81.
25. Raman N, Kulandaisamy A, Thangaraja C, Manisankar P, Viswanathan S, Vedhi C, *Trans. Met Chem.*, 2004; 29, 129.
26. Howlader M B H., Islam M S., Synthesis of some Ni(II) complexes containing 4-substituted benzylidene(4-benzyloxy)benzohydrazone ligand. *Indian J. Chem. A.* 2007; 46, 440-444.
27. Hamilton T D., Papaefstathion G S., MacGillivray L R., Bis Chelation and anion effects involving a molecule

constructed in the organic solid state using molecular templates. *Etter Transactions*, 2005; 1, 2-5.
28. Shakthi S., Mishra P M., Mishra S K., Jha A K., Synthesis and characterization of complexes of 2-hydroxy-3-nitroacetophenyl thiocarbazone with some 3d transition metals, *Asian Journal of Chemistry*, 2010; 22, 5013-5018.
29. Raman N., Mitu L., Sakthivel A., Pandi M S S., Studies on DNA Cleavage and antimicrobial screening of transition metal complexes of 4-aminoantipyrine derivatives of N_2O_2 type. *J. Iran. Chem. Soc.*, 2009; 6, 737-746.
30. Lever A B P., Inorganic Electronic spectroscopy, 2nd edition, Elsevier, New York, 1968.
31. Munde A S., Shelke V A., Jadhav S M., Kirdant A S., Vaidya S R., Shankarwar S G., Chondhekar T K., Synthesis, Characterization and Antimicrobial activities of some transition metal complexes of Biologically Active Asymmetrical Tetradentate Ligands. *Adv. Appl. Sci. Res.*, 2012, 3(1), 175.
32. Pelczar M J., Chan E C S., Krieg N R., Microbiology. McGraw-Hill, New York USA, (1996).
33. Mane P S., Shirodkar S G., Arbad B R.,Chondhekar T K., Synthesis, Characterization of manganese(II), Cobalt(II), nickel(II) and copper(II) complexes of schiff base derivatives of dehydroacetic acid. *Indian J. Chem.*, 2001; 40 A, 648-651.
34. Mishra L., Singh V K., Co(II) , Ni(II), Cu(II) and Zn(II) complexes with Schiff base derived from 2-aminobenzimidazoles and pyrazolycarboxaldehyde. *Indian J. Chem* .1993; 32A, 446-457.
35. Monks A., *et al*: Feasibility of high flux anticancer drug screen using a diverse panel of cultured human tumour cell lines. *Journal of the National Cancer Institute*, 1991; 83, 757-766.

How to cite this article:
Kirubavathy SJ, Velmurugan R, Parameswari K and Chitra S: Synthesis, characterization and biological evaluation of Cu(II), Co(III) and Fe(III) complexes of 2-benzoyl-3-(nitrophenyl)quinoxaline. Int J Pharm Sci Res 2014; 5(6): 2508-17.doi: 10.13040/IJPSR.0975-8232.5(6).2498-07