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SYNTHESIS AND TESTING OF METAL COMPLEXES OF QUINOXALINE BASED SCHIFF BASES FOR ANTIMICROBIAL AND ANTICANCER ACTIVITIES

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ABSTRACT: The compound 3-chloro-2-hydrazine quinoxaline was condensed with 2-furaldehyde to derive a Schiff base 2-furaldehyde-2-(3-chloro-2-quinoxalinyl) hydrazone (FCCQH).The ligand and also its complexes with VO (IV), Cr (III), Mn (II), Fe (III), Co (II), Ni (II), Zn (II), and Pd (II) have been synthesized and characterized by elemental analysis, magnetic studies, thermal analysis, infrared spectra, UV-visible spectroscopy and Electron Spin Resonance data. The ligand 2-furaldehyde-2-(3-chloro-2-quinoxalinyl) hydrazone [FCCQH] acts as a neutral, bidentate one towards VO(IV), Zn(II), and Pd(II) coordinating through free C=N nitrogen and oxygen of furan ring and as tridentate one towards Cr(III), Mn(II), Fe(III), Co(II), and Ni(II) complexes coordinating additionally through nitrogen of quinoxaline ring C=N. The complexes have been screened for antibacterial activity towards *staphylococcus aureus* (gram +ve), *Escherichia coli* (gram -ve) bacteria, antifungal activity towards *fusarium oxysporum* and anticancer activities of the compounds were evaluated by MTT assay on HeLa (cervical cancer) cell lines. While the antimicrobial activity profiles of the complexes are, by and large quite encouraging, the anticancer activity exhibited by Ni (II) and Pd (II) complexes are highly impressive.

INTRODUCTION: Quinoxalines are a class of fused six-membered nitrogen heterocyclics containing two nitrogens in mutually para dispositions. These compounds have a wide range of applications in pharmacology, bacteriology and mycology [1-5]. Quinoxaline and its derivatives have received attention as complexing agents owing to the presence of two potentially metal binding nitrogen centers at 1,4 positions [6-13]. Schiff bases constitute a special class of compounds; these compounds have played a central role as chelating agents for a large number of metal ions and are further associated with a variety of applications. They are also used in pigments, dyes and polymer industries.

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In biological front, these serve as model compounds of several vitamins and enzymes [14, 15] and have also been projected as promising pesticides, fungicides and bacteriocides. These compounds, in addition, possess a wide spectrum of medicinal properties and have been found to be active against influenza, leprosy, tuberculosis, malaria, and certain kinds of cancer.

The biological activity of organic compounds having potential donor sites is often attributed to their ability to chelate metal ions present in the biosystem; in many cases, the metal ion association exerts a synergistic effect on the activity of the free ligand.

Despite the fact that these compounds and their derivatives have potent donor groups, the studies directed towards exploring the ligational behaviour of them are limited. Hence, we report, herein, the synthesis and characterization of VO(IV), Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), and Pd(II) complexes with 2-furaldehyde-2-(3-chloro-2-quinoxalinyl) hydrazone [FCCQH] **(Fig.1)**, followed by their screening for antimicrobial and anticancer activities.

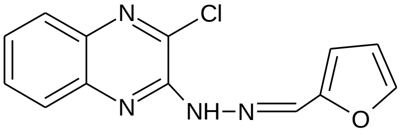


Fig.1

MATERIALS AND METHODS:

All the chemicals used were of AR or BDH grade. VO (IV) complex of the ligand was prepared taking its sulphate, Mn (II), Co (II), Ni (II), and Zn (II) complexes taking respective metal acetates and Cr (III), Fe (III) and Pd (II) complexes with their chlorides.

The elemental analyses were carried out by Carlo Erba 1108 elemental analyser at CDRI, Lucknow, India. Conductance measurements were made in DMF at 10^{-3} M concentration on a Digisun digital conductivity meter DI 909 model calibrated with 0.1 M KCl. The magnetic susceptibilities of the complexes were recorded on a Faraday balance (CAHN-7550-03) at room temperature using Hg $[Co(NCS)_4]$ as the standard.

Diamagnetic corrections were applied using Pascal's constants. The infrared spectra of the ligands and the metal complexes were recorded in KBr pellets in the range 4000 – 400 cm^{-1} on Perkin Elmer-BX spectrophotometer, and thermograms of metal complexes were taken on Mettler Toledo Star System. The electronic spectra of the metal complexes in DMF were recorded on Elico SL-159 UV-Visible spectrophotometer. The JEOL FEIX ESR spectrometer operating in the frequency range 8.8-9.6GHz was employed in recording the ESR spectra of VO (II) complexes in DMF solution at LNT. The complexes were further screened for antimicrobial and anticancer activity on HeLa (cervical cancer) cell lines.

Preparation of the ligand:

3-Chloro-2-hydrazinequinoxaline (I) was prepared according to a reported method. The ligand FCCQH was synthesized by adding I (0.01mole) in small lots to a stirred solution of 2-furaldehyde (0.01 mole) (Fluka) in DMF (10 ml) at room temperature. On completion of addition, a clear solution was obtained and on continuous stirring for a further period of 2 hours, a bulk yellow coloured compound was obtained which was filtered, washed with water and recrystallized from $CHCl_3$ and hexane. Melting point: 128-130^{o}C

Preparation of the metal complexes:

The metal complexes were prepared by combining methanolic or aqueous methanolic solution of the metal salt and methanolic solution of the ligand in 1:2 mole ratio and refluxing the mixture on a water bath for 2-3 hours. The solid that resulted, was filtered, washed with water, hot methanol and ether and dried in vaccum over fused $CaCl_2$.

Antibacterial activity:

Nutrient agar medium (M001) was obtained from Himedia, Mumbai and agar-agar from Bacto, Mumbai. Stainless steel borer of 0.6 mm diameter was used for making cups in the experiment. Nutrient agar medium was sterilized at 15 psi pressure for 20 min, in an autoclave at 121^{0}C. Petri plates were sterilized in hot air oven at 160^{0}C for one hour. Test organisms used for antibacterial screening were: *Staphylococcus aureus* (gram +ve) (MTCC-96) and *Escherichia coli* (gram –ve) (MTCC-118).

Sterilized nutrient agar medium (100ml) was cooled to around 40^{0}C. It was seeded with 50μl of 18h test organism. To each of the labelled petri plates, 27ml of the medium was transferred. The medium was allowed to solidify by allowing the plates in the laminar air flow bench for 30 min. Solutions of standard and test substances (50μl) were added into the cups. The plates were kept at room temperature for 2.5 hours to facilitate diffusion of the substances from the cups. The petri plates were then kept in inverted position in an incubator maintained between 32-35^{0}C, for 18 h. After the incubation period, the plates were observed for zone of inhibition.

Antifungal assay:

Asthana and Hawkers medium (Glucose 5.0g, KNO_3 3.5g, KH_2PO_4 1.75g, $MgSO_4$ 0.75g Agar-Agar 20.0g and a pinch of Rose Bengal) was taken and sterilized at 15 psi for 15 min. Then, the compound (0.1mg/ml acetone) was added in aseptic conditions in each petri plate. Sterile petri plates were allowed to cool for solidification. After solidification, the test fungus was inoculated in the center of the petri plate. After 3 days, the growth of the organism was recorded. A control was maintained without adding the test compounds. The activity of the compound was assayed by comparing the growth of the fungus in the compound and in the control.

Anticancer assay:

The anticancer assay of the compounds at concentrations 3μg/ml and 30μg/ml against A_{2780} ovarian cancer cell line was made employing MTT (3- (4, 5 – dimethylthiazole – 2 - yl) – 2, 5 - diphenyl-tetrazoliumbromide) assay.

Cell culture: HeLa (cervical cancer)

Cell number for subculture: one million cells for flask (30ml capacity)

Cell loading into plate: 1000-2000 cells per well (96-well plate)

Drug solutions: 5μM to 130μM.

MTT (3- (4, 5-dimethylthiazole - 2-yl) - 2, 5 - diphenyltetrazoliumbromide) measures the metabolic activity of the viable cells. The assay is non-radioactive and can be performed entirely in a micro titer plate (MTP). It is suitable for measuring cell proliferation, cell viability or cytotoxicity. The reaction between MTT and 'mitochondrial dehydrogenase' produces water-insoluble formazan salt. Procedure involves culturing the cells in a 96-well micro titer plate, and then incubating them with MTT solution for approximately 2 hours. During incubation period, viable cells convert MTT to a water-insoluble formazan dye. The formazan dye in the MTP is solubilized and quantified with an ELISA plate reader. The absorbance directly correlates with the cell number. This is applicable for adherent cells cultured in MTP.

RESULTS AND DISCUSSION:

The ligand FCCQH and the metal complexes are insoluble in water, slightly soluble in methanol and fairly soluble in dimethylformamide. The metal complexes are stable at room temperature and non-hygroscopic but they decompose on heating without melting. All the complexes are coloured and are electrolytic in dimethylformamide, the molar conductance of VO(IV) complex corresponding to 1:1 type, of Cr(III) and Fe(III) complexes to 1:3 type and of Mn(II), Co(II), Ni(II), Zn(II), and Pd(II) complexes to 1:2 type **(Table:1)**

The magnetic studies made on the complexes indicate that VO(IV), Cr(III), Mn(II), Fe(III), Co(II), and Ni(II) complexes are paramagnetic corresponding to one, three, five, five, three and two unpaired electrons respectively and that the Zn(II) and Pd(II) complexes are diamagnetic **(Table:1)**

TABLE 1: PHYSICO-CHEMICAL CHARACTERISTICS OF SCHIFF BASE LIGAND AND ITS METAL COMPLEXES

Ligand and Metal complex	Colour	Percent				Molar conductance	μ_{eff} B.M
		M	C	H	N	ohm^{-1} cm^{-2} mol^{-1}	exptl
FCCQH	Brown	---	56.67 (57.26)	3.13 (3.33)	20.19 (20.55)	----	----
$[VO(FCCQH)_2]SO_4$	Brown	6.91 (7.19)	43.56 (44.08)	2.37 (2.56)	15.51 (15.82)	72	1.71
$[Cr(FCCQH)_2]Cl_3$	Yellowish green	7.11 (7.39)	43.87 (44.37)	2.86 (2.58)	16.21 (15.92)	220	3.81
$[Mn(FCCQH)_2](OAC)_2$	Dark red	7.32 (7.65)	50.55 (50.16)	3.30 (3.37)	15.28 (15.60)	132	5.69
$[Fe(FCCQH)_2]Cl_3$	Dark brown	7.61 (7.89)	43.96 (44.13)	2.45 (2.56)	15.62 (15.84)	218	5.72
$[Co(FCCQH)_2](OAC)_2$	Orange red	8.07 (8.16)	49.44 (49.88)	3.27 (3.34)	15.32 (15.51)	129	4.68
$[Ni(FCCQH)_2](OAC)_2$	Orange red	7.95 (8.13)	50.25 (49.89)	3.34 (3.35)	15.31 (15.52)	131	2.98
$[Zn(FCCQH)_2](OAC)_2$	Yellow	8.79 (8.97)	49.12 (49.44)	3.25 (3.32)	15.12 (15.37)	132	---
$[Pd(FCCQH)_2]Cl_2$	Orange	14.62 (14.73)	42.85 (43.21)	2.43 (2.51)	15.33 (15.50)	126	---

Thermal studies of the selected metal complexes namely those of VO(IV), Cr(III), Mn(II), Fe(III), Zn(II), and Pd(II) indicate that they are thermally stable to different temperatures. They lose weight on heating almost in a continuous manner attaining constancy in weight at different temperatures, for example, VO (IV) complex above 620°, Cr(III) complex above 740°, Mn(II) complex above 900°, Fe(III) and Zn(II) complexes above 660° and Pd (II) complex above 680°C. The percent weight loss as computed from the thermograms of the complexes suggests that the final product of decomposition in all the cases, corresponds, within the permissible experimental error, to the respective metal oxide.

The structures of the compounds have been appropriately characterized and confirmed using spectroscopic data.

IR spectral data (Table-2)

The ligand FCCQH displays a broad, medium intensity band at 3432 cm^{-1} attributed to free νN-H [16]. This band remains almost unshifted in the spectra of the complexes indicating non-participation of nitrogen of this group in coordination. Further, the ligand reveals bands at 1630 cm^{-1} due to free ν C=N, and at 1580 cm^{-1} due to ring ν C=N. While both the bands undergo lower shift by about 20-30 cm^{-1} in the Cr (III), Mn (II), Fe (III), Co (II) and Ni (II) complexes, only the former does so in VO (IV), Zn (II) and Pd (II) complexes.

Further, a small intensity band at 887 cm^{-1} in the ligand due to ν C-O has been lower shifted by about 20 cm^{-1} in all the complexes indicating that furan oxygen is involved in coordination. This suggests that the ligand acts as a neutral, bidentate one bonding through nitrogen of azomethine group and oxygen of furan ring in VO(IV), Zn(II) and Pd(II) complexes and as a tridentate one coordinating additionally through nitrogen of quinoxaline ring C=N in Cr(III), Mn(II), Fe(III), Co(II), and Ni(II) complexes.

TABLE-2: IR ABSORPTION FREQUENCIES (cm^{-1}) OF FCCQH AND ITS METAL COMPLEXES

S. No	Compound	νN-H	νC=N (Free)	νC=N (quinoxaline ring)	νC-O (furan cyclic)	νC-Cl
1	FCCQH	3432	1634	1579	887	767
2	VO-FCCQH	3432	1600	1581	863	763
3	Cr-FCCQH	3432	1608	1550	868	763
4	Mn-FCCQH	3432	1600	1556	863	761
5	Fe-FCCQH	3431	1608	1560	865	765
6	Co-FCCQH	3432	1601	1556	864	754
7	Ni-FCCQH	3432	1602	1558	862	766
8	Zn-FCCQH	3432	1598	1578	867	762
9	Pd-FCCQH	3433	1602	1581	864	767

Electronic spectral data:

The electronic spectral frequencies observed for the complexes along with ligand field parameters for the Co(II) and Ni(II) complexes are given in **Table 3.** These frequencies may be assigned, in the increasing order, to the transitions as mentioned below.

VO(IV) complex : $^2B_2 \rightarrow {}^2E$, $^2B_2 \rightarrow {}^2B_1$ and $^2B_2 \rightarrow {}^2A_1$
Cr(III) complex : $^4A_{2g} \rightarrow {}^4T_{2g}$, $^4A_{2g} \rightarrow {}^4T_{1g}(F)$ and $^4A_{2g} \rightarrow {}^4T_{1g}(P)$
Mn(II) complex : $^6A_{1g} \rightarrow {}^4T_{1g}(G)$, $^6A_{1g} \rightarrow {}^4T_{2g}(G)$ and $^6A_{1g} \rightarrow {}^4E_g(g)$
Fe(III) complex : $^6A_{1g} \rightarrow {}^4T_{2g}(G)$, $^6A_{1g} \rightarrow {}^4T_{2g}(G)$ and $^6A_{1g} \rightarrow {}^4E_g(g)$,
$^6A_{1g} \rightarrow {}^4A_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}(d)$
Co(II) complex : $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$
Ni(II) complex : $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$
Pd (II) complex : $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$ and $^1A_{1g} \rightarrow {}^1E_g$

Based on these transitions and the other data observed, square pyramidal geometry for the VO(IV) complex, octahedral geometry for Cr(III), Mn(II), Fe(III), Co(II) and Ni (II) complexes square planar geometry for the Pd(II) complex and tetrahedral geometry for the d^{10} Zn (II) complex have been proposed. Further, the ligand field parameters: 10 DQ, B and β obtained for the Co(II) and Ni(II) complexes indicate that the metal-ligand bond in them is covalent in nature.

TABLE 3: ELECTRONIC SPECTRAL DATA OF THE METAL COMPLEXES OF FCCQH

S.No	**Metal complex**	**Frequencies (cm^{-1})**			**ν_2/ν_1**	**10DQ cm^{-1}**	**B cm^{-1}**	**β**
		ν_1	**ν_2**	**ν_3**				
1	VO-FCCQH	14480	16660	25500	--	---	---	---
2	Cr-FCCQH	16500	23000	32000	--	---	---	---
3	Mn-FCCQH	13120	19180	24610	--	---	---	---
4	Fe-FCCQH	12500	15600	20000	--	---	---	---
5	Co-FCCQH	9300	16220	22980	1.74	6918	753	0.775
6	Ni-FCCQH	9530	14200	24300	1.49	9530	661	0.642
7	Pd-FCCQH	14970	18650	23360	1.24	---	---	---

ESR Spectra:

The ESR spectral parameters calculated for the VO(IV) complexes using appropriate methods and equations are presented in **Table-4**. The spectrum of the VO(IV) complex is well resolved with eight parallel and eight perpendicular components due to hyperfine coupling with vanadium nucleus having I = 7/2. The g and A values observed for the VO(IV) complex is in agreement with those generally for a vanadyl complex with a square pyramidal geometry with $g_{||} < g_{\perp} < g_e$ (where g_e is free electron value) indicating that the unpaired electron is in the d_{xy} orbital with ^2B as the ground state.

TABLE-4: ESR PARAMETERS OF VO (IV) COMPLEX:

Complex	**$g_{\|\|}{}^{*}$**	**$g_{\perp}{}^{*}$**	**$g_{av}{}^{*}$**	**$A_{\|\|}*10^4$ (cm^{-1})**	**$A_{\perp}*10^4$ (cm^{-1})**	**$A_{av}*10^4$ (cm^{-1})**
VO-FCCQH	1.95	1.99	1.98	141	65	90

BIOLOGICAL ACTIVITY:

Antibacterial activity (Table-5)

In vitro antibacterial activity of compounds was evaluated by seeded plate technique against two strains 1) *Staphylococcus aureus* (gram +ve) (MTCC-96) and 2) *Eschrichia coli* (gram -ve) (MTCC-118), using streptomycin as the standard. The compounds were tested at each of concentrations 0.1mg/ml and solubilized in DMSO and were prepared by dilusion with acetone.

The results of the antimicrobial activity of the ligand and metal complexes screened against the microorganisms indicate that the ligand FCCQH does not exert activity on the microorganism as are its Mn, Fe and Co Complexes. However, the Cr, Zn, Ni and Pd complexes are found active to a different level.

Table 5: Antibacterial activity of the compounds:

Solvent: Acetone]

Concentration: 0.1mg/ml

S.No	**Compound**	**Zone of inhibition(mm)**	
		***Staphylococcus aureus* (Gram+ve)**	***Escherichia Coli* (Gram -ve)**
1	FCCQH	----	----
2	VO-FCCQH	----	5.5
3	Cr-FCCQH	4.0	3.0
4	Mn- FCCQH	----	----
5	Fe- FCCQH	----	----
6	Co- FCCQH	----	----
7	Ni- FCCQH	3.0	----
8	Zn- FCCQH	2.5	4.0
9	Pd- FCCQH	----	6.0
10	Streptomycin sulphate(standard)	15.0	14.5

Antifungal activity (Table-6):

In vitro antifungal activity of compounds was evaluated by seeded plate technique against fungus Fusarium Oxysporium using Flucanozole as the standard. The compounds were tested at concentration 0.1mg/ml in DMSO.

The results indicate that the ligand is moderately active towards the microorganism and most of the metal complexes are either more active than or as active as the ligand. While the Cr and Mn complexes show similar activity as the ligand, the other metal complexes are more active, with the Zn complex having the highest.

TABLE 6: ANTIFUNGAL ACTIVITY OF THE COMPOUNDS

Solvent: Acetone

Concentration: 0.1mg/ml

S.No	**Compound**	**Percentage of inhibition *Fusarium oxysporum***
1	Medium(Control)	****
2	FCCQH	***
3	VO- FCCQH	**
4	Cr- FCCQH	***
5	Mn- FCCQH	***
6	Fe- FCCQH	**
7	Co- FCCQH	*
8	Ni- FCCQH	*
9	Zn- FCCQH	-----
10	Pd- FCCQH	**

****	No inhibition (Full growth)
***	25 % inhibition
**	50 % inhibition
*	75 % inhibition
----	100 % inhibition

Anticancer activity:

In vitro anticancer activity of the compounds was evaluated by MTT assay at concentrations 3µg/ml and 30µg /ml against A_{2780} ovarian cancer cell. The complexes have been tested for their anticancer activity on HeLa (Cervical Cancer) cell line in vitro using MTT colorimetric assay. Of all the complexes tested, only the Ni(II) and Pd(II) complexes are found to have considerable activity. The results of cytotoxic activity of these to complexes and cisplatin at concentration 3 µg/ml are:

Ni-FCCQH	89.71
Pd-FCCQH	78.6
Cisplatin	3.63

The results indicate that the Pd is more cytotoxic than the Ni complexes.

CONCLUSIONS: The syntheses, characterization, antimicrobial and anticancer activities of the ligand FCCQH and its complexes have been carried out. The geometry of the complexes has been assigned based on physico-chemical data. Pertaining to the antimicrobial activity, the complexes have been found more active and with regard to anticancer activity, the Ni and Pd complexes are found quite promising.

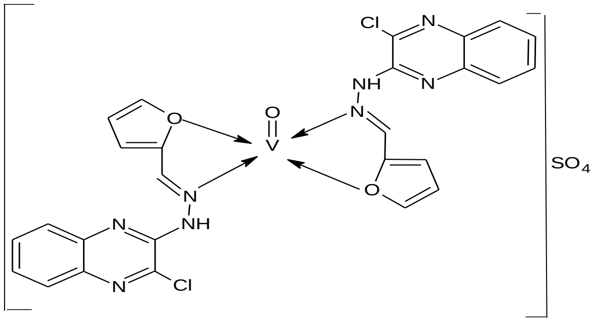
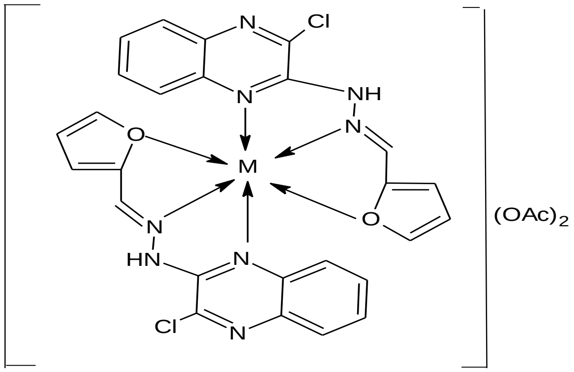


FIG 2: STRUCTURE OF VO(IV)- FCCQH



M= Mn, Co, Ni

FIG 3: STRUCTURE OF Mn(II), Co(II) and Ni(II) COMPLEXES OF FCCQH

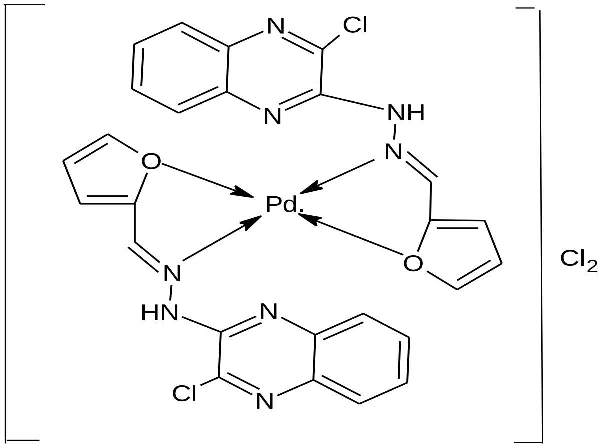


FIG 4: STRUCTURE OF Pd(II)- FCCQH

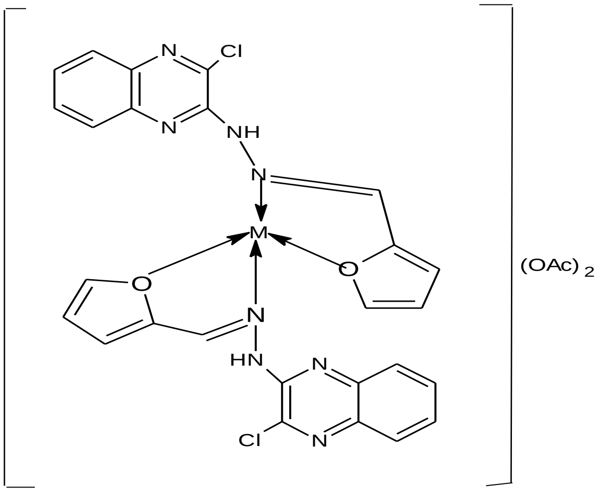


FIG 5: STRUCTURE OF Zn(II) COMPLEX OF FCCQH

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