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Synthesis, Characterization, Single Crystal XRD and biological evaluation of Nickel(II)salen sulphadiazine complex

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Abstract

Nickel(II)salen sulphadiazine complex was prepared and characterised by the spectral studies such as FT-IR, UV-Vis, NMR and single crystal XRD. The Nickel(II) complex was screened for *in-vitro* antimicrobial activities against various test organisms *Aeromonas hydrophila*, *Serratia marcescens*, *Bacillus licheniform*, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Aspergillus niger* and *Candida albicans* by the well diffusion method cultured on Sabrouds dextrose agar as medium and *in-vitro* anticancer activity against the human breast cancer cell line HeLa. The NiO obtained by the thermal decomposition of Ni (salen) sulphadiazine complex was characterised using TEM images and their SAED pattern.

Keywords

Nickel (II), sulphadiazine, antimicrobial, anticancer, thermal decomposition.

INTRODUCTION

Schiff bases are condensation products of primary amines with carbonyl compounds, namely aldehyde or ketone and they were first reported by Schiff in 1864[1]. The common structure of these compounds is the azomethine group with a general formula R-C=N- in which alkyl, aryl, cyclo alkyl or heterocyclic groups may be variously substituted, and are also known as imines or azomethines. Several studies [2 - 4] showed that the presence of a lone pair of electrons in the sp^2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance. Because of the relative easiness of preparation, synthetic flexibility, and the special property of C=N group. The C-N linkage is essential for biological activity, antibacterial, antifungal, anticancer and anti-malarial activities [5, 6]. Schiff bases are generally excellent chelating agents especially when a functional group like –OH or –SH is present close to the azomethine group so as to form a five or six membered ring with the metal ion. Schiff base compounds are very popular ligands because of their easy formation and rich coordination chemistry with a large variety of metal ions those have allowed their use as catalysts in different asymmetric reactions [7, 8]. Several compounds incorporating piperazinyl guanidine, when condensed with salicylaldehyde were found to exhibit cardiovascular and vasodepressive activity [9]. Versatility of Schiff base ligands and biological, analytical and industrial applications of their complexes make further investigations in this area highly desirable.

Sulfadiazine is a sulfonamide with well known antibacterial activities and used clinically as a topical agent either alone or in combination with other compounds in the treatment of wound and burn infections. Interest in the metal complexes of sulfadiazine is due to its use as

pharmaceuticals. At present, the possibility of using metal complexes of sulfadiazine as antimicrobial agents has received some attention. However, the literature on the chemistry of Schiff base complexes derived from sulpha drugs especially their structural characteristics, is rather incomplete.

In continuation of our efforts in the search of antimicrobial agents and to check with its cytotoxicity, we have synthesized nickel salen complex with sulphadiazine and screened them for antimicrobial and cytotoxic activities.

EXPERIMENTAL

Materials and Methods

All chemicals used were of analar grade. All the reagents, starting materials and solvents were purchased commercially from sigma aldrich and used without any further purification. Apparatus and materials involved in synthesis were clean and dry. The melting points were recorded on a *Raaga 840* melting point apparatus. Microanalytical data of the compounds were recorded in the *Elementar Vario EL III* CHN Analyser. The FT-IR spectrum was recorded on a *Shimadzu* spectrophotometer in the range 4000-500 cm^{-1}. The electronic spectrum was recorded by using a *Shimadzu* UV Vis. spectrophotometer (double beam) in the range of 200– 800 nm. Conductivity measurements were carried out by using *Elico* Conductivity Bridge, (Conductivity meter). ^{1}H and ^{13}C NMR spectra were recorded on a *Jeol* 400 MHz Spectrometer TMS as an internal standard. X-ray diffraction for the [Ni(salen)]sulphadiazine complex was made on a *Bruker APEX-2* X-Ray diffractometer with graphite monochromated *Mo*-Kα radiation (λ = 0.71073 Å). The crystal structure was solved by direct methods. Structure refinements were performed by full matrix least squares procedures using *SHELXTL (XS)* on F^2.

Synthesis of [Ni(salen)]sulphadiazine complex

Synthesis of Ni complex is done by refluxing ethanolic solution of the following reaction mixtures, sulphadiazine (0.005mol), salicylaldehyde (0.005mol), ethylenediamine (0.001 mol) and nickel nitrate (0.001mol) for 5 hrs. After completion of the reaction the complex obtained was filtered, washed with ether and dried. Yield: 72%. Red crystalline Solid, For C_{26} H_{24} N_6 Ni O_4 S, anal. calcd., % : C, 49.22; H, 4.20; N, 14.60, Found, % : C, 49.20; H, 4.15; N, 14.69.

Determination of X-ray crystal structure

A Bruker *APEX-2 X-ray* (three-circle) diffractometer was employed for crystal screening, unit cell determination, and data collection. The X-ray radiation employed was generated from a Mo sealed X-ray tube (Kα= 0.71073Å with a potential of 40 kV and a current of 40 mA) fitted with a graphite monochromator in the parallel mode (175 mm collimator with 0.5 mm pinholes). A solution was obtained readily using *SHELXTL (XS)* [10]. Hydrogen atoms were placed in idealized positions and were set riding on the respective parent atoms. All non-hydrogen atoms were refined with anisotropic thermal parameters. The structure was refined (weighted least squares refinement on *F*2) to convergence [11]. Olex2 was employed for the final data presentation and structure plots.Supplementary material for the crystal structure has been deposited with the Cambridge Crystallographic Data (no: 1041536; deposit@ccdc.cam.ac.uk or http://ccdc.cam.ac.uk)

Antibacterial Activity

The sulphadiazine has potency to cure the wound infection also acts as antimicrobial agent, so that the complex of the sulphadiazine also expected to possess increased biological activity [12, 13]. The antimicrobial activity of sulphadiazine and the title complex was studied

using the procedure as reported in the literature [14]. On chelation the polarity of the metal ion is reduced to a greater extent, thereafter it enhances the activity of the complex. [15].

Anticancer study - Cell treatment procedure and MTT assay

Cytotoxicity of the compounds were carried out on human breast cancer cell line (MCF-7) was obtained from National Centre for Cell Science (NCCS), Pune India. For the screening experiment, the cells were seeded onto 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 for 24hrs prior to the addition of the compounds. The compounds were dissolved in DMSO and diluted in the respective medium containing 1% fetal bovine serum (FBS). After 24hrs the medium was replaced with the respective medium with 1% FBS containing the compounds at various concentrations and incubated at 37°C under conditions of 37°C, 5% CO_2, 95% air and 100% relative humidity for 48rs. Triplication was maintained and the medium not containing the compounds served as control. After 48hrs, 15 µL of MTT (5 mg mL^{-1}) in phosphate buffered saline (PBS) was added to each well and incubated at 37°C for 4hrs. The medium with MTT was then removed and the formed formazon crystals were dissolved in 100 µL of DMSO. The absorbance was then measured at 570nm using microplate reader. The % cell inhibition was determined using the following formula

$$\%\ \textbf{Cell Inhibition} = \textbf{100} - \textbf{Abs}\ (\textbf{sample}) / \textbf{Abs}\ (\textbf{control})\ \textbf{x100}.$$

Nonlinear regression graph was plotted between % Cell inhibition and Log concentration and IC_{50} was determined using Graph Pad Prism software [16, 17].

RESULTS AND DISCUSSION

The title complex is red crystalline solid stable in air allowing physical measurements, dissolves in DMF to give stable solutions at room temperature. Its melting point is 240 – 245°C and is uncorrected. The molar conductance of the metal complexes (10^{-3} M) was found to be 0.12 $Scm^{-1}mol^{-1}$ proving its non-electrolytic behavior [18, 19]. The analytical data of the ligand and the complex is in good agreement with the experimental values and the molecular formula for the complex is found as [Ni ($C_{16}H_{14}N_2O_2$)($C_{10}H_{10}N_4O_2S$)] and it is shown in experimental section.

FT-IR Spectra

The FT-IR spectral data give valuable information regarding the nature of the functional group attached to the metal atom. A characteristic azomethine linkage of (-HC=N-) is observed at 1573 cm^{-1} and (>C=N-) in pyrimidine ring is assigned for the band that appears at 1488 cm^{-1}. A band appears at 3333 cm^{-1} in Ni complex confirming the presence of $–NH_2$ in the complex. The band at 1154 cm^{-1} is due to symmetric vibration of SO_2 [20, 21].

The FT-IR-spectra of complex gives the band for the occurrence of non-ligand band which is seen at 646 cm^{-1} of M-N bond. No change in the band appearing at 1488 cm^{-1} shows that >C=N- linkage for the pyrimidine ring is not involved in co-ordination. The SO_2 bands in both sulphadiazine and complex remain unchanged, so that we can come to know that there is no participation of SO_2 group in coordination. No band coordination around 3700 cm^{-1} indicates there is no water molecule present in the complex.

Electronic spectral data

The electronic spectral data is in relevance with the proposed geometry of complex. The electronic spectrum of Ni(II) complex (Fig. 1) shows absorption at respective regions. The zero magnetic moment indicates diamagnetic Ni(II) complex with square planar geometry. Square planar complex of Ni(II) have no affinity for axial ligand coordination in solution [22]. The electronic absorption spectral bands of the complex Ni(II) is recorded over the range 200-800 nm in DMF and its λ_{max} value also assigned and it exhibits two absorption band at 450 nm and 420 nm. These may be assigned to the transition $^3A_{1g} \rightarrow {}^3B_{2g}$ and $^3A_{1g} \rightarrow {}^3E_g$ [23]. The characteristic d-d transition band of square planar Ni(II) complex over the range 440 nm is seen. The observed bathochromic shift in the position of visible band is analogous to weaker ligand field energy which is responsible for red shift for the complex[24].

NMR spectral data

The ^1H NMR spectrum of the Ni complex exhibits signals at following ranges. The ^1H NMR spectra of the complex shows triplet at δ 3.43 ppm for the hydrogens attached to C-8 and C-9. Two multiplets around δ 6.50 to 7.63 ppm correspond to the aromatic protons in the complex. In the pyrimidine ring a doublet appears for the hydrogen of C-18 and C-20 at δ 7.9 ppm which differs from azomethine hydrogen analog to (-CH=N-) group. For the hydrogen of C-19 a triplet appears at δ 7.17 ppm. The singlet at δ 8.48 ppm is due to (-NH-) attached to the SO_2 group. Free NH_2 of the sulphadiazine shows a signal at δ 5.97 ppm .

^{13}C NMR spectra provide further support for the structural probability of the complex. The signals for C-18 and C-20, C-19, C-4 and C-13, C-2 and C-15, C-8 and C-9 appears at δ

157.2 ppm, δ 112 ppm, δ 120.3, δ 133.5 and δ 163.9 ppm respectively. Aromatic carbons give signals at δ 115.4 ppm for C-23 & C-25 and δ 124.9 ppm for the C-22 & C-26. The azomethine carbons (C-1 & C-16) attached to nitrogens gives signal at 163.94 ppm [25]. The ^{1}H-NMR and ^{13}C NMR spectra of the Ni(II) complex is shown in Fig. 2 and 3 respectively.

Thermal analysis (TGA/DTA) of [Ni(salen)]sulphadiazine complex

The thermogravimetric analysis gives information about the thermal stability of the complex and suggests a general scheme for thermal decomposition. In the present investigation, heating rates were suitably controlled at 10°C/min under nitrogen atmosphere and the weight loss was measured from the ambient temperature upto 800°C. Ni (II) complex of the template synthesis shows the mass loss in accordance with elimination of certain group. At 100º C there is no depression in group which reveals that there is no water molecule in the complex both outer and inner co-ordination sphere. There is a gradual depression up to 280º C with loss of 5% of mass which may be due to the elimination of sulphurdioxide gas. Then above 280º C a heavy mass loss of 61% is seen till 390º C corresponds to the loss of co-ordinated and non co-ordinated part of the sulphadiazine leaving the metal oxide as residue. The thermogram of the Ni(II) complex is depicted in Fig. 4.

Single crystal X-ray diffraction of [Ni(salen)]sulphadiazine complex

The complex crystallizes in the triclinic system with space group P-1, Z=2 with the unit cell dimensions a=9.031(2)Å , b=10.927(3) Å, c=14. 580(4) Å, α=69.853(2)°, β=73.048(3)°, γ= 67. 912(2)°. The structure of the Ni complex consists of [Ni(salen)] and one unco-ordinated

sulphadiazine moiety. Ni(II) is co-ordinated by two nitrogen and two oxygen from the salen ligand forming a square planar geometry and the sulphadiazine moiety remains unco-ordinated. The bond lengths for imino nitrogen atom are Ni(1)-N(1) and Ni(1)-N(2) are 1.843(2) and 1.845(2) respectively and the bond lengths for Ni-O i.e. Ni(1)-O(1) and Ni(1)-O(2) are 1.8479(17) and 1.8429(17) respectively. The different bite angles around the square plane i.e. O(1)-Ni(1)-N(1), N(1)-Ni(1)-N(2), N(2)-Ni(1)-O(2), O(2)-Ni(1)-O(1), N(1)-Ni(1)-O(2) and N(2)-Ni(1)-O(1) are 94.87(8), 86.08(10), 94.65(9), 84.38(7), 179.05(8) and 178.49(8) respectively show that there are slight distortions. No molecule of water is found in the hydrated form. One molecule of sulphadiazine is found unco-ordinated. Table 1 and 2 shows Crystal data and structural refinement parameters and **s**elected bond length (Å) and bond angle (°) respectively. The ORTEP representation and the packing diagram of the title complex is shown in Fig. 5 and Fig. 6 respectively.

TEM and SAED pattern

The NiO nanoparticle was synthesized at 600ºC using Ni complex as precursors and their properties studied with the help of transmission electron microscope and SAED pattern. Fig. 7 show the TEM images of the synthesized NiO nanoparticle, with an image magnification. Fig. 8 demonstrates the SAED pattern of the synthesized NiO nanoparticle.

Antimicrobial activity

The antibacterial activity of the Ni(II) complex was tested against the bacteria *Aeromonas hydrophila, Serratia marcescens, Bacillus licheniform, Pseudomonas aeruginosa* and *Acinetobacter baumanii* respectively by the well diffusion method using Mueller Hinton agar

nutrient as the medium. The antifungal activities were screened for the organisms *Aspergillus niger* and *Candida albicans* by the well diffusion method cultured on Sabrouds dextrose agar as medium. The inhibition zones were developed, at which the concentration was inferred as very good activity for *Pseudomonas aeruginosa* and *Acinetobacter baumanii* bacterial strains at all concentration levels, 22-26 mm and moderate activity for other strains, can be seen in Figure 9. The results of antibacterial and antifungal screening has been compared with the standard Ciprofloxacin and Clotrimazole in each case. The minimum inhibitory concentration of the title complex against *Pseudomonas aeroginosa* and *Acinetobacter baumanii* are 250 and 125µg/ml respectively. In the case of fungal strains *Aspergillus niger* and *Candida albicans* the complex shows moderate activity. The inhibition zones are shown in Figure 10. The increased activity of the Ni(II) complex than sulphadiazine can be explained based on chelation theory[26, 27].

Anticancer activity

In cancer study, complex is screened for human breast cancer cell at different concentration. The inhibitory concentration (IC_{50}) was noted in the series of dilutions, which gives appropriate cell inhibition % and rise in the graph (Fig. 11). For the Nickel Salen complex the % inhibition property increases to the increase in concentration as 2.2380 to 47.9145. IC_{50} is employed to stand for the cytotoxicities of the compounds against the cancer cell lines; the smaller the IC_{50} value in the same condition is, the higher the cell growth inhibitory potency. The average IC_{50} value was calculated by Graph Pad Prism software is 116 µM which is moderate level of inhibition [28, 29]. The IC_{50} value of the nickel nitrate and sulphadiazine was checked and found to be >100 µM. DMSO when used as control without test sample, it does not exhibit any cytotoxic activity against cancer cell line .The data suggest that the compounds are less cytotoxic

on HeLa cells at moderate concentrations(200-50µg/ml). It may be noted that the typical IC_{50} values for the commercial drug cisplatin falls in the range 1.34-2.20 µM on HeLa cells.

The importance of metal based anticancer drugs increased abundantly after the success of cisplatin and its successors which are presently promising candidates in clinical evaluation. The mode of action in the anticancer drug is through the formation of metal-DNA adducts and through cellular redox homeostasis. In this case, the Ni(II) complex is more stable with ethylenediamine ligands and kinetically inert having a lower reactivity with biomolecules[30]. The importance of such work lies in the possibility that the next generation of metal complexes might be more efficacious as anticancer agents. A detailed investigations with tailoring new complexes and analyzing their stability under biological conditions could be helpful in designing more potent anticancer agents for the therapeutic use in the future.

Conclusion

In this study, Ni(II) salen sulphadiazine complex has been synthesized and characterized by various spectral techniques and the structure was confirmed using single crystal X-ray diffraction studies. Ni(II) is coordinated with two nitrogen atoms and two oxygen atoms forming square planar geometry and the sulphadiazine moiety remains unchanged. The synthesised complex has been screened for their in-vitro antimicrobial activity against various test organisms and found to be good. The in-vitro anti-cancer study shows the IC_{50} value of 116µM against the human breast cancer cell lines.

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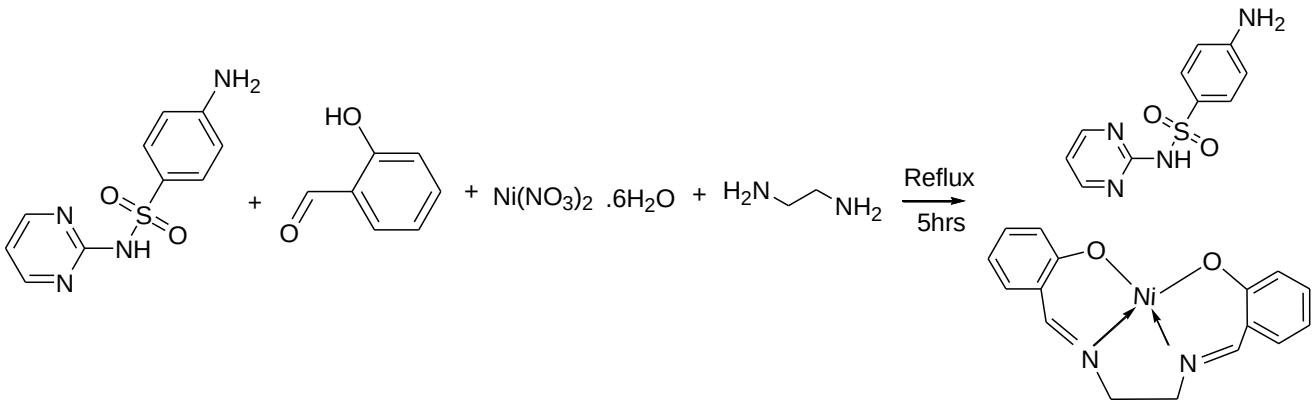
Table 1: Crystal data and structural refinement parameters

Empirical formula	C_{26} H_{24} N_6 Ni O_4 S
Formula weight	575.28
Temperature	110.15 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.031(2) Å
	b = 10.927(3) Å
	c = 14.580(4) Å
	α= 69.853(2)°
	β= 73.048(3)°.
	γ = 67.912(2)°.
Volume	1229.7(5) $Å^3$
Z	2
Density (calculated)	1.554 Mg/m^3
Absorption coefficient	0.921 mm^{-1}
F (000)	596
Crystal size	0.523 x 0.417 x 0.325 mm^3
Theta range for data collection	1.514 to 27.455°
Index ranges	-11<=h<=11, -14<=k<=14, -18<=l<=18
Independent reflections	5553 [R(int) = 0.0175]
Completeness to theta	25.242° 99.8 %
Max. and Min. transmission	0.7456 and 0.6255
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	5553 / 33 / 343
Goodness-of-fit on F2	1.061

Final R indices [I>2 sigma (I)]	R1 = 0.0398, wR2 = 0.0950
R indices (all data)	R1 = 0.0433, wR2 = 0.0972
Largest diff. peak and hole	0.873 and -0.858 e.Å^{-3}

Table: 2. Selected bond lengths and bond angles

Ni(1)-O(1)	1.8479(17)
Ni(1)-O(2)	1.8429(17)
Ni(1)-N(1)	1.843(2)
Ni(1)-N(2)	1.845(2)
O(2)-Ni(1)-O(1)	84.38(7)
O(2)-Ni(1)-N(2)	94.65(9)
N(1)-Ni(1)-O(1)	94.87(8)
N(1)-Ni(1)-O(2)	179.05(8)
N(1)-Ni(1)-N(2)	86.08(10)
N(2)-Ni(1)-O(1)	178.49(8)
C(1)-O(1)-Ni(1)	126.71(15)
C(16)-O(2)-Ni(1)	127.31(17)
C(7)-N(1)-Ni(1)	126.94(17)
C(7)-N(1)-C(9)	118.4(2)
C(9)-N(1)-Ni(1)	114.57(19)
C(8)-N(2)-Ni(1)	114.7(2)
C(10)-N(2)-Ni(1)	127.08(18)



Scheme 1. Synthesis of Nickel (II) complex

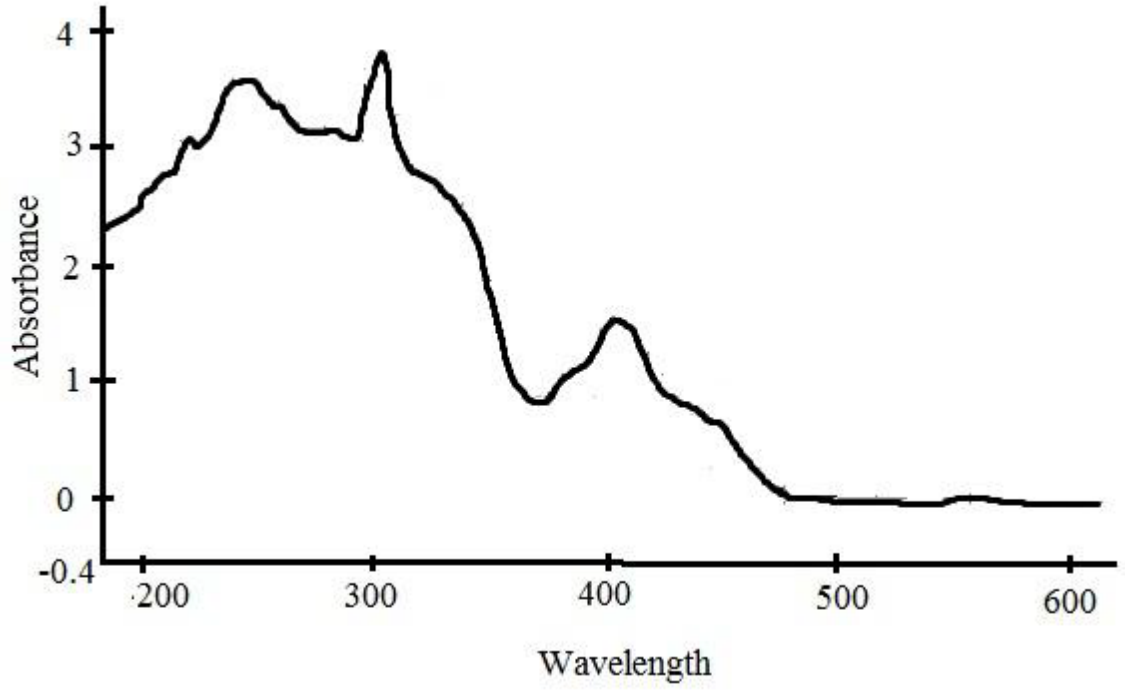


Fig. 1. Electronic Spectrum of Ni(II) complex

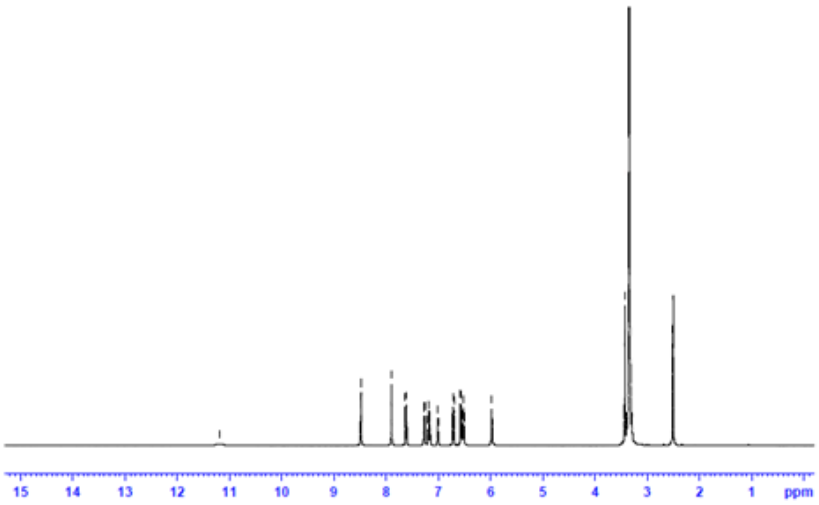


Fig. 2. H^1 NMR Spectra [Ni(salen)]sulphadiazine complex

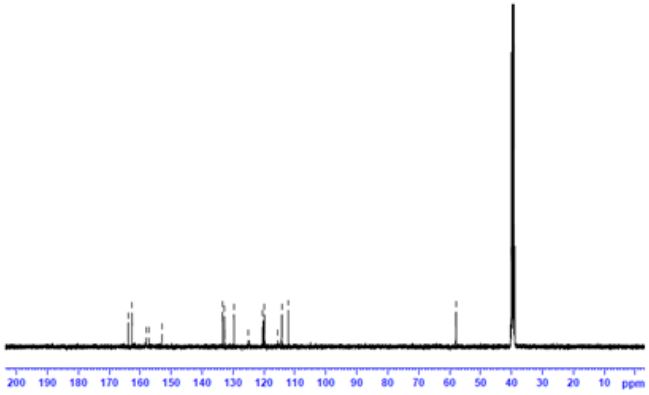


Fig. 3. C^{13} NMR spectra of [Ni(salen)]sulphadiazine complex

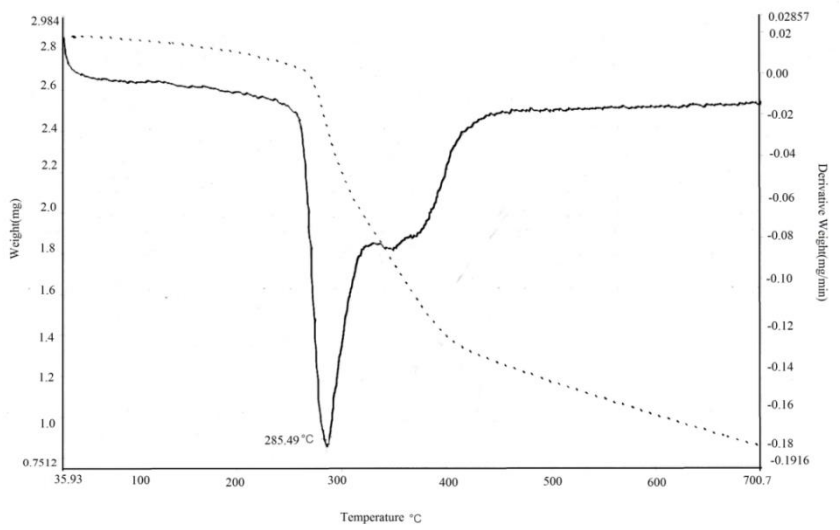


Fig. 4. Thermogram of Ni(II) complex

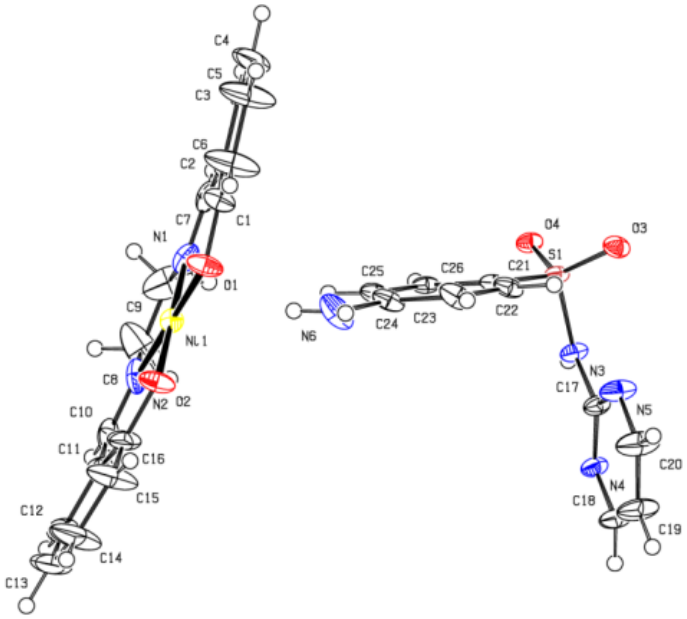


Fig. 5. ORTEP diagram of [Ni(salen)]sulphadiazine complex.

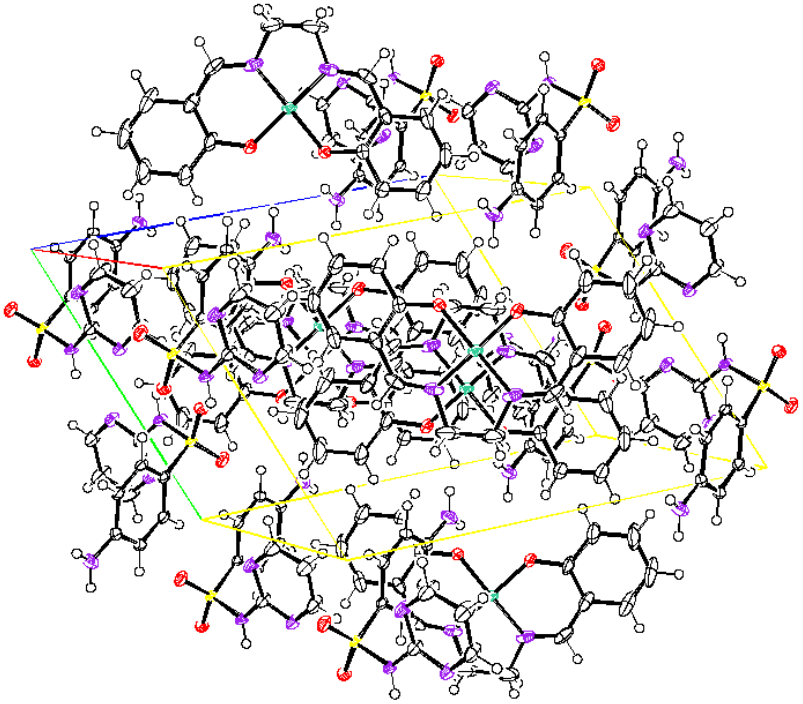


Fig. 6. Packing diagram of [Ni(salen)]sulphadiazine complex

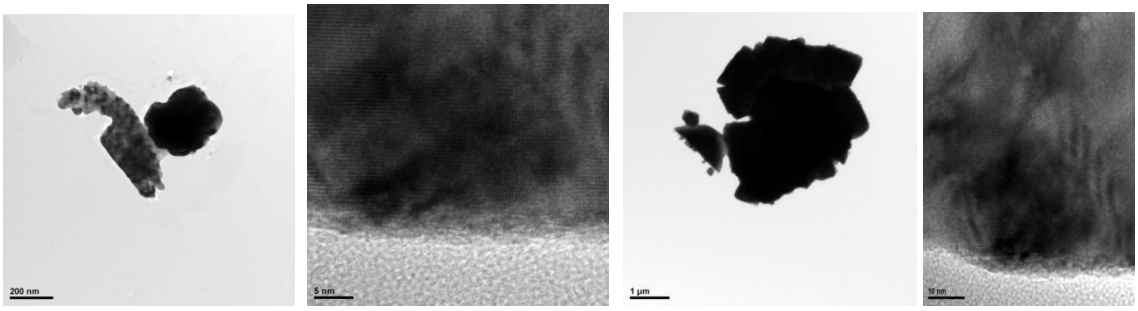


Fig. 7. TEM images of NiO nanoparticle

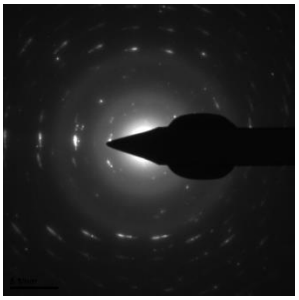


Fig. 8. SAED pattern of NiO particle

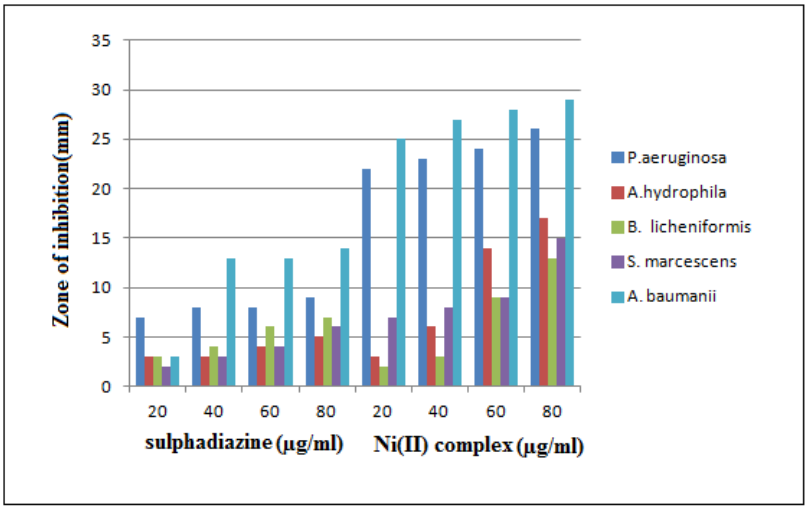


Figure 9: Anti bacterial activity of complex

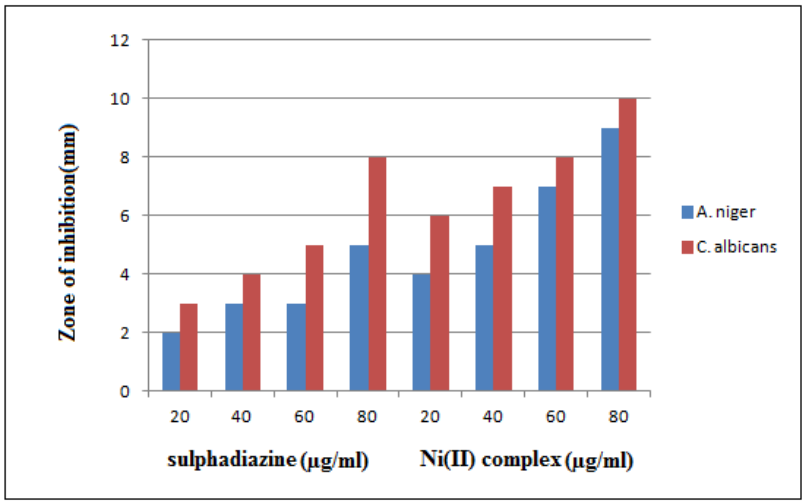


Figure 10: Anti fungal activity of complex

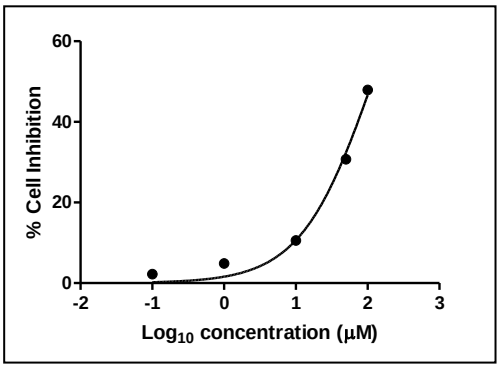


Fig. 11. Graph between % Cell inhibition and Log concentration of Ni(II) complex