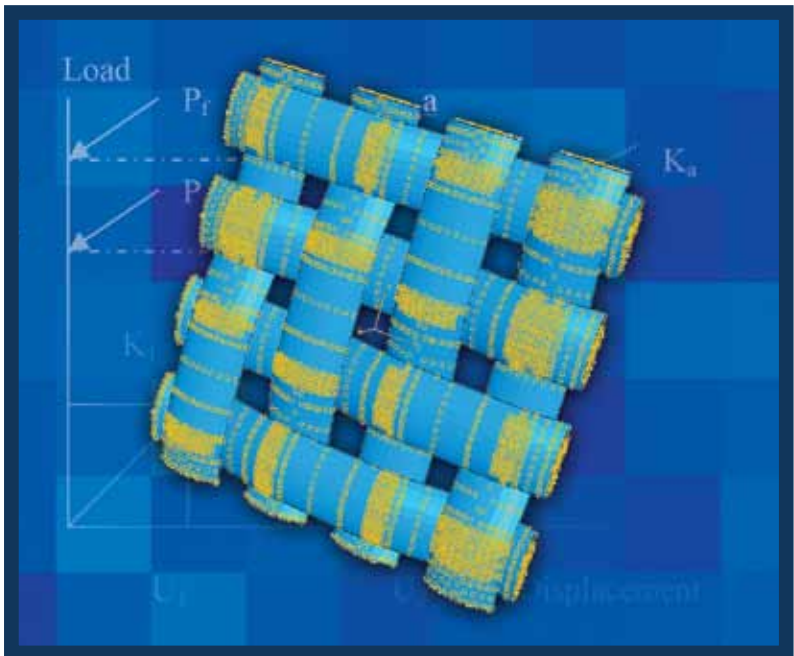


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Mohd Abdul Fatah Abdul Manan

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Mohd Asrul Hafiz Muhamad

Syed Nazmi Sayed Mohamed

Synthesis, Characterization and Biological Activity of Nitrogen-Oxygen-Sulfur (NOS) Transition Metal Complexes Derived from Novel S-2,4-dichlorobenzylidithiocarbamate with 5-fluoroisatin

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ABSTRACT

*A novel Schiff base containing nitrogen-oxygen-sulfur (NOS) donor atoms formed from the condensation reaction of S-2,4-dichlorobenzylidithiocarbamate (S-2,4BDTC) with 5-fluoroisatin has been synthesized. Complexes of cobalt(II), nickel(II), copper(II), zinc(II) and cadmium(II) with this Schiff base have been prepared and characterized using elemental analysis and various physico-chemical techniques. In the cobalt(II) and nickel(II) complexes the Schiff base behaves as a uninegatively charged tridentate nitrogen-oxygen-sulfur (NOS) chelating ligand, bonding through the azomethine nitrogen, thiolate sulfur and carbonylic oxygen of the isatin moiety. However, in the copper(II), zinc(II) and cadmium(II) complexes the Schiff base behaves as a nitrogen-sulfur (NS) bidentate chelating ligand, bonding through the azomethine nitrogen and thiolate sulfur. The Schiff base and the metal complexes were evaluated with respect to antimicrobial activity, which was performed in relation to two selected pathogenic microbials (*Bacillus subtilis* and *Pseudomonas aeruginosa*). It*

was observed that only the zinc Schiff base complex exhibited strong activity against the Bacillus subtilis bacteria with an inhibition zone of 25 mm.

Keywords: *Metal complexes, S-2-4dichlorobenzylidithiocarbazate, 5-fluoroisatin, Schiff base, Biological activity*

Introduction

Dithiocarbazate, $\text{NH}_2\text{NHCS}_2^-$, is a chelating agent derived from the S-alkyl esters of dithiocarbazic acid; the metal complexes of which have been extensively studied over the past two decades [1-3], not only because of their behaviour as ligands in transition metal complexes, but also have been shown to exhibit interesting physico-chemical and potentially chemotherapeutic properties [1-3, 29, 31, 34-37, 47, 51, 50, 54, 55, 60].

Isatin is an endogenous compound isolated in 1988 and reported to possess a wide range of activities involving the central nervous system [4-7]. Schiff bases and Mannich bases derived from isatin have been reported to possess antibacterial [8-14, 17-19, 39], antifungal [11-13, 17, 19], antiviral [10, 14-16, 35], anti-HIV [11-13, 17, 19], antiprotozoal [20,21], and antihelminthic activities [22, 23].

Variety of halogenated compounds particularly fluorine-containing aromatic compounds have drawn much attention because of their biological activities [24]. Many of them are used as pharmaceuticals and pesticides or have found use as precursors for the synthesis of biologically active compounds. In 2006, SU11248 (Sutent), a 5-fluoro-3-substituted-2-oxoindole, was approved by the US FDA for the treatment of gastrointestinal stromal tumors [25] and advanced renal-cell carcinoma [26]. Tyrindoleninone (6-bromo-2-methylthio-3*H*-indol-3-one), a brominated precursor to tyrian purple, isolated from the egg masses of the Australian mollusk *Dicathais orbita* have been found to exhibit cytotoxic activity [27].

Although much attention has been directed to the study of Schiff and Mannich bases derived from isatin [8, 9, 11, 12, 14, 16-18, 33, 38, 39, 42, 49, 52, 55], no investigations have appeared in the literature to describe the Schiff bases derived from dithiocarbazate with 5-haloisatins. Furthermore, only limited studies have been performed on dithiocarbazato Schiff bases comprising of nitrogen-oxygen-sulfur (NOS) donor sequences. Therefore, as part of ongoing research into Schiff bases derived from dithiocarbazates, it is reported herein the synthesis,

characterization and antibacterial activity of Schiff base derived from novel S-2,4-dichlorobenzoyldithiocarbamate with 5-fluoroisatin.

Experimental

Preparation of S-2,4-dichlorobenzoyldithiocarbamate (S-2,4-BDTC)

A potassium hydroxide solution is prepared by dissolving 11.4 g (0.2 mole) in 70 ml of 90% ethanol. To this solution, 10 g (0.2 mole) of hydrazine hydrate is added and the resultant mixture cooled in an ice-salt bath to 0°C. 15.2 g (0.2 mole) of carbon disulfide is added dropwise at a rate of 40 drops/min with constant stirring for one hour using a mechanical stirrer at a rate of 700 rotation/min, whilst maintaining the solution below 5°C. Consequently two distinct layers form; the lower oil layer is light-brown and separated from the top layer using a separation funnel. The oil is then dissolved in 40% ethanol (60 ml) and maintained below 5°C using an ice-bath to prevent decomposition of the dithiocarbamic acid. 39.1 g (0.2 mole) of 2,4-dichlorobenzyl chloride is added dropwise with vigorous stirring, supplied by a mechanical stirrer, to the cooled mixture. The white product is S-2,4-BDTC, which is filtered, washed with ethanol, dried, recrystallized and finally stored in a desiccator.

Preparation of Schiff Base (S-2,4-5-FISA)

The Schiff base is synthesized by dissolving 2.67 g (0.01 mole) of S-2,4-dichlorobenzoyldithiocarbamate (S-2,4-BDTC) in 50 ml of hot 95% ethanol to which an equimolar quantity (1.65 g, 0.01 mole) of 5-fluoroisatin is added and also dissolved. The mixture is heated for 20 minutes then cooled to 0°C in an ice bath. The product is filtered, washed with cold ethanol, recrystallized from 95% ethanol and then dried over silica gel.

Preparation of the S-2,4-5-FISA Metal Complexes

0.1 mole of metal acetate is dissolved in 50 ml of hot 95% ethanol along with 0.2 mole of the Schiff base. The resultant mixture is stirred and heated for 20 minutes yielding a precipitate which is cooled, filtered, washed with ice cold ethanol and dried over silica gel. The metal salts

used in this work are copper (II) acetate, nickel (II) acetate tetrahydrate, cadmium (II) acetate, cobalt (II) acetate and zinc (II) acetate. The yields of these syntheses are between 55-70%.

Physical measurements

Microanalyses for carbon, hydrogen, nitrogen and sulfur were performed using a LECO CHNS-932 and the IR spectra were performed using KBr pellets on a Perkin-Elmer FT IR 1750X spectrophotometer over the wavenumber range 4000-400 cm^{-1} . Mass spectra were recorded on a Shimadzu Gas Chromatography-Mass Spectrometer (GCMS-QP5050A) with direct sample injection. The ^1H NMR spectrum of the Schiff base was recorded on a JOEL-JNM ECA 400 MHz spectrometer and the molar conductance of 10^{-3} M metal complex dimethyl sulfoxide (DMSO) solutions were determined at 29°C using a Jenway 4310 conductivity meter and a dip cell with a platinum electrode. Magnetic susceptibilities at room temperature were measured using a Sherwood Scientific MSB-AUTO magnetic susceptibility balance and UV-Vis spectra were performed on a Shimadzu UV-2501 PC Recording Spectrophotometer over the wavelength range of 1100-200 nm. Metal identification was performed on a Perkin-Elmer Plasma 1000 Emission Spectrometer.

Determination of Biological Activity

Two pathogenic microbials were selected to be used in the evaluation of the biological potential of the Schiff base and metal complexes. The selected micobials were *Bacillus subtilis* (wild type – B29) – Gram-positive and *Pseudomonas aeruginosa* (60690) – Gram-negative.

Qualitative Antimicrobial Assay

The antimicrobial activity of the compounds were qualitatively determined with respect to a modified disc diffusion method [28]. A microorganism lawn was prepared by pipetting and evenly spreading inoculum (10^{-4} ml, adjusted turbidometrically so that the colony forming units (cfu) had a concentration of 10^5 - 10^6 cfu/ml) on agar set in Petri dishes, which used nutrient agar (NA) for the bacteria and potato dextrose agar (PDA) for the fungi. 6 mm diameter Whatman No. 1 filter paper discs were

impregnated with the metal complex DMSO solutions (100 mg/ml) and dried under sterile conditions. The dried discs were then placed on top of the inoculated agar surfaces; the plates were inverted and incubated for 24 h at 37°C. Antimicrobial activity was evaluated with respect to the presence of clear inhibition zones around the impregnated paper discs.

Results and Discussion

Physico-Chemical Data

Physico-chemical properties of the Schiff base and the metal complexes are presented in Table 1 below. The (C, H, N and S) results obtained are in good agreement with those calculated for the predicted formulae, furthermore the ICP-OES analysis provides the metal concentrations present in the complexes. All the metal complexes exhibited a metal to ligand ratio of 1:2, which is in good agreement with the CHNS elemental analysis. The melting points of the Schiff base and metal complexes are sharp ($\pm 1^\circ\text{C}$) indicating the purity of the prepared compounds.

Table 1: Physico-chemical Data of the Schiff Base and the Metal Complexes

Compound	Colour	Melting Point (°C)	% Found (Calc.)				
			C	H	N	S	Metal
S-2,4-5FISA	Yellow	234	46.20 (46.38)	2.32 (2.43)	10.04 (10.14)	15.21 (15.48)	-
Co(S-2,4-5FISA) ₂	Brown	272	43.04 (43.40)	1.88 (2.05)	9.13 (9.49)	14.18 (14.48)	6.97 (6.66)
Ni(S-2,4-5FISA) ₂	Dark brown	288	43.15 (43.41)	1.92 (2.05)	9.06 (9.49)	14.24 (14.49)	6.60 (6.63)
Cu(S-2,4-5FISA) ₂	Dark grey	241	42.98 (43.18)	1.89 (2.04)	9.21 (9.44)	14.15 (14.41)	6.97 (7.14)
Zn(S-2,4-5FISA) ₂	Dark orange	296	42.99 (43.09)	1.97 (2.03)	9.24 (9.42)	14.12 (14.38)	7.20 (7.33)
Cd(S-2,4-5FISA) ₂	Red	293	40.52 (40.93)	1.77 (1.93)	8.52 (8.95)	13.51 (13.66)	12.36 (11.97)

Fourier-Transform Infrared Data for the Schiff Base and the Metal Complexes

The IR spectral data for the Schiff base and the metal complexes is presented in Table 2.

Table 2: Infrared Data for the Schiff Base and the Metal Complexes

Compound	Bands (Wavelength, cm^{-1})				
	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}=\text{S})$	$\nu(\text{C}-\text{S})$	$\nu(\text{N}-\text{N})$
S-2,4-5-FISA	1689	1575	1071	–	1146
Co(S-2,4-5-FISA) ₂	1682	1569	–	992	1167
Ni(S-2,4-5-FISA) ₂	1678	1583	–	990	1161
Cu(S-2,4-5-FISA) ₂	1706	1586	–	938	1155
Zn(S-2,4-5-FISA) ₂	1706	1585	–	989	1163
Cd(S-2,4-5-FISA) ₂	1702	1593	–	982	1157

For the purposes of infrared analysis there are three key functional group bands, which are $\nu(\text{C}=\text{N})$, $\nu(\text{N}-\text{N})$ and $\nu(\text{C}=\text{O})$. The position of these bands enable comparative analysis to be performed, since the bands shift upon complexation with the metal ions. The IR spectrum of the ligands in the uncoordinated form exhibit a broad band in the 3500-3200 cm^{-1} region, which is attributable to N-H stretching. The presence of the NH group in the isatin ring in all the complexes makes it difficult to observe the disappearance of the $\nu(\text{N}-\text{H})$ band due to the deprotonated nature of the dithiocarbazate. The Schiff base contains a thione group ($\text{C}=\text{S}$) and an adjacent proton; it has been stated that the thione group ($\text{C}=\text{S}$) is relatively unstable in the monomeric form and tends to convert into the more stable C-S single bond through enethiolization when at least one hydrogen atom is adjacent to the $\text{C}=\text{S}$ bond [29]. The IR spectrum of the Schiff base does not contain a $\nu(\text{S}-\text{H})$ band at *ca.* 2570 cm^{-1} indicating that in the solid-state it exists in the thione form (Figure 1(a)), however in solution it exists in equilibrium with the thiol tautomeric form (Figure 1(b)).

The $\nu(\text{C}=\text{S})$ band at 1071 cm^{-1} observed for the free ligand is not present in the metal complex spectra, yet a $\nu(\text{C}-\text{S})$ band is observed at 992-938 cm^{-1} , which supports the suggestion that coordination is through the thione sulfur as a consequence of thiol tautomerization [30,31].

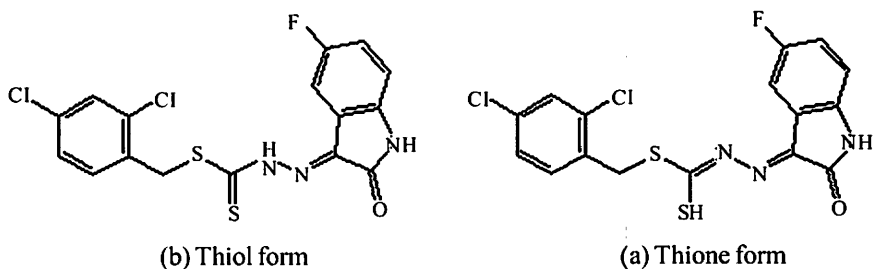


Figure 1: Thione-Thiol Tautomerization of the Schiff Base

The presence of the $\nu(\text{C}=\text{N})$, $\nu(\text{N}-\text{N})$ and $\nu(\text{C}=\text{O})$ bands at 1593-1569 cm^{-1} , 1167-1146 cm^{-1} and 1706-1678 cm^{-1} , respectively, indicate that the coordination of the Schiff base to the metal ion is *via* the azomethine nitrogen (1), the thiolate sulfur atom (2) and the carbonylic oxygen (3), Figure 2.

The $\nu(\text{C}=\text{N})$ band normally occurs around 1575 cm^{-1} , but upon complexation this wavenumber increases in all, but the Co(II) complex. It has been reported that the shifting of the free ligand azomethine $\text{C}=\text{N}$ band from higher to lower wavenumbers in the spectra of metal complexes is evidence of coordination between the thiosemicarbazone and dithiocarbazate sites to the metal ions *via* the azomethine nitrogen atom [32]. However, shifting of this band to both higher [33] and lower wavenumbers [34] has also been reported.

The hydrazinic $\nu(\text{N}-\text{N})$ band is found to shift to higher wavenumbers for all metal complexes further implying that metal ions coordinate through the azomethine nitrogen atom. The presence of bands at 1167 and 1161 cm^{-1} in the cobalt and nickel complexes indicate coordination of the Schiff base to the metal ion as a uninegatively charged tridentate chelating agent in its thiolate form. In the case of the copper, zinc and

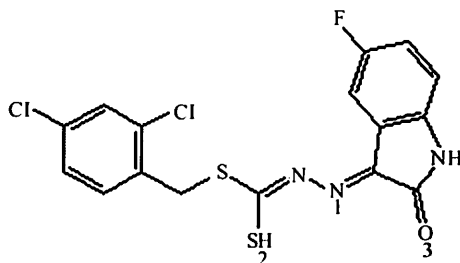


Figure 2: Schiff Base Coordination Sites

cadmium complexes, these bands appear at 1155, 1163 and 1157 cm^{-1} , respectively, suggesting coordination of the Schiff base to the metal ion as a uninegatively charged bidentate chelating agent. The shift of the $\nu(\text{N-N})$ band to higher and lower wavenumbers has been reported for other metal complexes with similar Schiff bases [35-37], which further supports the presented findings.

In the spectra of cobalt and nickel complexes, the carbonylic oxygen band is shifted to lower wavenumber indicating that coordination is between the carbonylic oxygen and the metal ions [38]. The shifting of the carbonylic oxygen bands to higher wavenumbers in the spectra for the copper, zinc and cadmium complexes indicates that the carbonylic oxygen is not strongly coordinated within these complexes [39].

Molar Conductance, Magnetic Data and Electronic Spectral Analyses of the Schiff Base and Their Metal Complexes

The molar conductivity of the metal complexes can be used to determine the number of ions present in a solution. Table 3 presents the molar conductivity for the metal complex DMSO solutions (10^{-3} M) at room temperature. The molar conductance values for the complexes are below those expected for 1:1 electrolyte complexes, which are normally in the range $50\text{-}70 \text{ }\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ [40], which indicates that the metal complexes are non-electrolytes. The non-electrolytic nature of the complexes also indicates that the ligand anion moieties have not dissociated. Furthermore, the non-electrolytic nature of the complexes prove that the Schiff base is coordinated to the metal ion as a uninegatively charged tridentate species *via* the azomethine nitrogen, thiolate sulfur and carbonylic oxygen atoms in

Table 3: Magnetic Susceptibility and Molar Conductivity of the Metal Complexes

Compounds	μ_{eff} (B.M) at 298K	Λ ($\Omega \text{ cm}^2 \text{ mol}^{-1}$)
$\text{Co}(\text{S-2,4-5-FISA})_2$	4.35	6.3
$\text{Ni}(\text{S-2,4-5-FISA})_2$	3.09	0.8
$\text{Cu}(\text{S-2,4-5-FISA})_2$	2.18	3.1
$\text{Zn}(\text{S-2,4-5-FISA})_2$	Diamagnetic	3.0
$\text{Cd}(\text{S-2,4-5-FISA})_2$	Diamagnetic	0.7

cobalt and nickel complexes, whereas in the copper, zinc and cadmium complexes the Schiff base coordinates to the metal ion as a uninegatively charged bidentate species *via* the azomethine nitrogen and thiolate sulfur atoms.

The magnetic susceptibility of the metal complexes at room temperature are presented in Table 3. The cobalt (II) complex exhibits paramagnetism with a value of 4.35 B.M.; the normal range for octahedral cobalt (II) complexes is 4.3–5.2 B.M. [41]. This indicates that the cobalt (II) complex is in an octahedral environment with a high-spin configuration [42] and the magnetic susceptibility of the complex also indicates the presence of three unpaired electrons per cobalt (II) ion, which is consistent with an octahedral environment [43,44].

The nickel (II) complex reported herein has a magnetic moment of 3.09 B.M. at room temperature, which is in the normal range (2.80-3.50 B.M.) for low-spin octahedral nickel (II) complexes according to the works of Mohamed *et al.* and Cotton *et al.* [45,46].

The magnetic susceptibility of the copper (II) complex exhibits paramagnetism with a room temperature magnetic moment of 2.18 B.M., which corresponds to the normal range for square planar copper (II) ions [47].

The zinc (II) and cadmium (II) complexes exhibit diamagnetism, since the d^{10} configuration of zinc (II) and cadmium (II) results in tetrahedral complexes since they are unlikely to form bridged dimeric square planar structures.

The electronic spectral excitation bands for the Schiff base and the metal complexes are presented in Table 4. The spectrum for the Schiff base exhibits bands at 262 nm and 383 nm, which may be attributed to $n \rightarrow \pi^*$ transitions in both the benzyl and indole rings and $\pi \rightarrow \pi^*$ transitions in the carbonyl, thione and azomethine groups, respectively [38]. The metal complexes bands in relation to the free ligand bands stated have shifted, thereby indicating that the chelation of the Schiff base to the metal ion.

The cobalt complex exhibits a band at 455 nm that corresponds to a charge transfer between a sulfur atom and a cobalt (II) ion, which indicates that there is coordination between the thiole sulfur and cobalt atoms. There are also three $d-d$ transition bands, which correspond to cobalt (II) with a high-spin octahedral geometry. These bands may be assigned as ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)(\nu_1)$ at 1000 nm, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(\nu_2)$ at 550 nm and

Table 4: Electronic Spectral Excitation Bands for the Schiff Base and the Metal Complexes

Compounds	UV-Vis spectra λ_{\max} , nm (Log ϵ mol ⁻¹ L cm ⁻¹)
S-2,4,5-FISA	262(4.24), 383(4.40)
Co(S-2,4,5-FISA) ₂	271(4.52), 382(4.36), 455(4.42), ≈550sh, ≈1000sh
Ni(S-2,4,5-FISA) ₂	271(4.52), 392(4.46), 492(4.40), ≈525sh, 933(1.83)
Cu(S-2,4,5-FISA) ₂	270 (4.51), 391(4.31), 436(4.32), ≈650sh
Zn(S-2,4,5-FISA) ₂	263(4.46), 463(4.46)
Cd(S-2,4,5-FISA) ₂	263(4.47), 462(4.46)

${}^4T_{1g} \rightarrow {}^4T_{1g}(P)(\nu_3)$ at 320 nm, respectively, in a distorted octahedral field [48, 49].

The presence of a ligand to metal charge transfer (LMCT) band at 492 nm in the electronic spectrum of the nickel (II) complex provides strong evidence that the nickel(II) ion is coordinated to the Schiff base *via* the sulfur atom. Sulfur to metal ion LMCT bands have also been observed and reported in the electronic spectra of nickel (II) thiosemicarbazones [50] and dithiocarbazates complexes [51, 52, 53, 54]. Six-coordinate nickel (II) complexes are expected to exhibit three electronic spectra bands corresponding to ${}^3A_{2g} \rightarrow {}^3T_{2g}$, ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ transitions. In the electronic spectrum for the nickel (II) complex, two *d-d* bands at 933 and 525 nm corresponding to the ${}^3A_{2g} \rightarrow {}^3T_{2g}(F)$ and ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ transitions, respectively, are observed, which is consistent with a six-coordinate octahedral geometry.

The electronic spectrum of the copper (II) complex exhibits a broad *d-d* band at *ca.* 650 nm and two intra-ligand bands at 391 and 270 nm, which may be attributed to a ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transition [55] and copper (II) thiosemicarbazone and dithiocarbazate coordinations, which exhibit S→Cu(II) charge-transfer bands at around 400 nm in their electronic spectra, respectively. The position of the *d-d* bands for this complex (Table 4) are similar to those of other square-planar copper (II) complexes with other related ligands, whose structures have been determined by X-ray diffraction [56]. Therefore the existence of this transition and the magnetic moment values presented in Table 3 provide sufficient evidence to confidently conclude that the geometry of the copper (II) complex is square planar [57].

The electronic spectra for the cadmium (II) and zinc (II) complexes only exhibit one intra-ligand band at 263 nm and S→M^{II} LMCT transitions at 462 to 463 nm, respectively. No *d-d* transitions are observed in either of the spectra due to the fully occupied *d* orbitals of the complexes themselves.

¹H NMR Data for the Schiff Base

¹H nuclear magnetic resonance spectra have been used to determine the structure of the organic ligands in DMSO; the important chemical shifts for which are presented in Table 5.

Table 5: ¹H NMR Data for the Schiff Base Derived from S-2,4-dichlorobenzylidithiocarbazate

¹ H NMR (δ, ppm)	SMISA
NH (dithiocarbazate)	13.95 (singlet, 1H)
NH (isatin ring)	11.36 (singlet, 1H)
Ar-H and pyrrole (isatin ring)	6.91-7.67 (multiplet, 7H)
S-CH ₂ -	4.60 (singlet, 2H)

The spectrum does not exhibit any resonance peaks near to 4.00 ppm, which could be attributed to the S-H proton, which strongly suggests that the thione tautomer is the dominant species in solution.

The signal at δ4.60 ppm may be attributed to the methylene hydrogen (CH₂), even though the theoretical value for methylene hydrogen is in the range of δ1.2-1.4 ppm [58]. The cause of the significant downfield shift for the Schiff base methylene hydrogen group is the deshielding effect of the close proximity electronegative sulfur and the aromatic ring. The singlet at δ13.95 ppm has been assigned to the secondary dithiocarbazate proton and the singlet at δ11.36 ppm has been tentatively assigned to the NH in the isatin ring pyrrole group. The isatin ring NH signal has been reported to appear further upfield than the NH of the dithiocarbazate as a consequence of intermolecular hydrogen bonding [49]. The cluster of signals found in the δ6.91-7.67 ppm region are associated with aryl protons, namely those found in the benzyl and pyrrole groups.

Mass Spectrum Analysis of the Schiff Base

The mass spectra analysis has been used in the determination of the molecular formula of the ligand and to predict its structure through the examination of the fragment ions. The loss of the NH group from 5-fluoroisatin yields a molecular ion of mass 399 m/z, whereas the loss of the CO group [59] gives a molecular ion of mass 386 m/z. The fragmentation of the parent molecular ion gives two characteristic peaks with m/z values of 90 and 78, as shown in Figure 3. The base peak, which is the most abundant ion formed during ionization, has a mass of

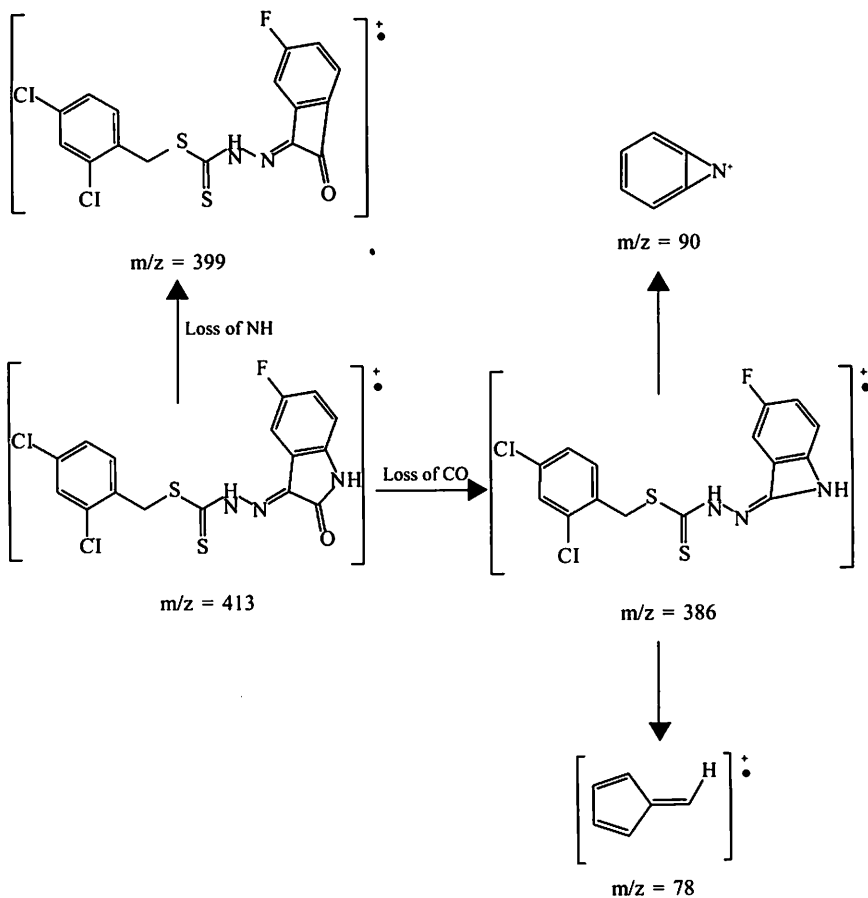


Figure 3: The Fragmentation of the Parent Molecular Ion, which Yields Two Characteristic Mass Fragment Peaks at 90 and 78 m/z

159 m/z and corresponds to the 2,4-dichlorobenzyl carbocation, which rearranges to form the more stable tropylium ion [58].

There are two further characteristic fragment peaks with masses 192 and 234 m/z, which are due to the fragmentation of *S*-2,4-dichlorobenzylthiocarbamate and 5-fluoroisatin, Figure 4.

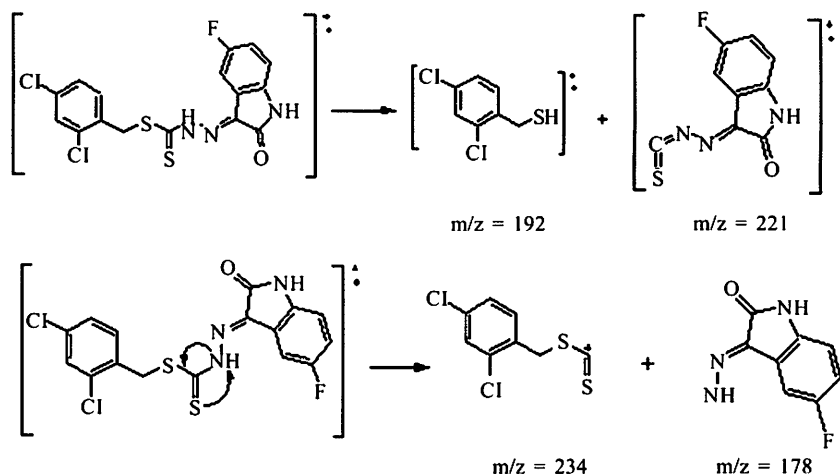


Figure 4: The Fragmentation of *S*-2,4-dichlorobenzylthiocarbamate and 5-fluoroisatin

Biological Activity

The Schiff base and metal complexes were screened for antimicrobial activity; the results for which are presented in Tables 6.

Antimicrobial Activity

The antimicrobial activity of the Schiff base and metal complexes was estimated with respect to the diameter of the clear inhibition zones. Compounds for which the inhibitory zone is less than 10 mm are considered to be weakly active, those with diameters in the range 10-15 mm in diameter are classified as moderately active and if the zone is more than 15 mm then the compounds are classified as strongly active with respect to the tested bacteria [61]. It was observed that the Schiff base and most of the metal complexes exhibited little or inhibitive activity (zone diameter < 15 mm) with respect to the tested bacteria.

Table 6: Qualitative Antimicrobial Assay (100 mg/ml)

Sample	Bacterial strain	
	B29	60690
S-2,4-5FISA	8	9
Co(S-2,4-5FISA) ₂	8	7
Ni(S-2,4-5FISA) ₂	9	8
Cu(S-2,4-5FISA) ₂	8	8
Zn(S-2,4-5FISA) ₂	25	7
Cd(S-2,4-5FISA) ₂	8	8
Streptomycin (Standard)	20	20

B.Subtilis -*Bacillus subtilis* - wild type (B29)

P.aeruginosa - *Pseudomonas aeruginosa* (60690)

Weak: 10 mm in diameter

Moderately active: 10-15 mm in diameter

Strongly active: 15 mm in diameter [60]

The zinc (II) complex exhibits strong activity against the *Bacillus subtilis* bacteria with the inhibition zone of 25 mm in diameter, which may be attributed to the effect of chelation [62]. Chelation reduces the polarity of the metal ion through the partial sharing of positive charge with donor groups and possible p electron delocalization within the chelation structure. Cell walls and membranes are made up of cellulose, lipids and proteins which are preferred for metal ion interaction. In addition, the cell wall of bacteria also contains peptidoglycan, a polymer of *N*-acetyl glucosamine, *N*-acetyl muramic acid and amino acids which provide suitable sites for metal ion binding. Chelation increases the lipophilic character of the chelate. The toxic reaction within the pores due to the interaction between metal ion and lipid may lead to the breakdown of the permeability barrier of the cell resulting in interference with the normal cell processes. This reaction only can take place if the geometry and charge distribution around the molecule are compatible with the geometry and charge distribution around the pores of the bacterial cell wall [62, 63].

Besides chelation, hydrophobic interactions also may play an important role on the antibacterial activity. Such interaction may involve the side chains of the *S*-2,4-dichlorobenzylidithiocarbamate (*S*-2,4-BDTC) Schiff base interacting with the bacteria cell protein molecule thereby inhibiting the formation of the cell wall, which results in an incomplete cell wall and

the loss of vital cellular material and the subsequent death of the cell [64]. The inhibitory potency also depends on the electron affinity of the substituted groups in isatin. A computational study showed that compounds with nonpolar and more electron withdrawing groups such as fluoro, chloro and bromo are significantly more potent than the compound with an amino group [65].

In addition, the presence of electron donor groups can contribute to the enhancement of biological activity [65]. This was also observed in this antibacterial study, whereby the carbonyl group in the zinc (II) appears not to coordinate to the metal and thus was more potent against *Bacillus Subtilis*, thus supporting the suggestion that the donor atoms play an important role in biological activity. Heterocyclic ligands could be promising candidates as bactericides since they always tend to interact either with nucleoside bases (even after complexation with metal ion) or with biologically essential metal ions present in the biosystem which may lead to the formation of higher coordination number complexes [63].

Conclusion

A novel nitrogen-oxygen-sulfur (NOS) Schiff base; S-2,4-5-FISA, has been successfully synthesized and characterized using various physico-chemical and spectroscopic techniques. This Schiff base was reacted with cobalt (II), nickel (II), copper (II), zinc (II) and cadmium (II) acetate to produce five transition metal complexes. The Schiff base behaves as a versatile chelating agent exhibiting variable dentate ability in accordance with the metal ion centres. The Schiff base in the cobalt (II) and nickel (II) complexes behaves as a uninegatively charged tridentate nitrogen-sulfur-oxygen (NOS) chelating ligand bonding through the azomethine nitrogen, thiolate sulfur and carbonylic oxygen of the isatin moiety. By comparison the Schiff base in the copper (II), zinc (II) and cadmium (II) complexes behaves as a nitrogen-sulfur (NS) bidentate chelating ligand bonding through the azomethine nitrogen and thiolate sulfur.

¹H NMR spectrum for the Schiff base indicates that the ligand retains the more stable thione tautomeric form in solution and along with the mass spectrum analysis confirms that the Schiff base is fully synthesized. All the metal complexes are non-electrolytes in dimethyl sulfoxide (DMSO) solution indicating the absence of ionic bonding in all cases. The magnetic moments and electronic spectra indicate that the copper (II) complex is paramagnetic with either a square planar or distorted

square planar geometry, whereas the cobalt (II) and nickel (II) complexes are paramagnetic with distorted octahedral geometry. The zinc (II) and cadmium (II) complexes are diamagnetic in a tetrahedral geometry as a consequence of possessing a d^{10} configuration and are hence unlikely to form bridged dimeric square planar structures.

The Schiff base and their complexes have been evaluated with respect to their biological activity against two pathogenic microbials; namely *Bacillus subtilis* and *Pseudomonas aeruginosa*. Only the zinc (II) complex was found to be active against *Bacillus subtilis* bacteria with an inhibition zone diameter of 25 mm.

With continued research more data can be acquired, which will contribute to and supplement available information to further elucidate the selectivity patterns of Schiff bases and the metal complexes it forms through the use of molecular modeling and quantitative structure-activity relationships (QSAR).

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