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RESEARCH ARTICLE

Synthesis, Spectral Characterisation and Cytotoxic Evaluation of Substituted Sulfonamide Schiff Bases

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Abstract

Objectives: To synthesize Schiff bases i.e 4-((2-hydroxybenzylidene)-amino–N-(5-methyl-1,2-oxozol-3- yl)benzene sulphonamide (L1), 4-((2-hydroxy benzylidene)-amino-N-(thiazol-yl)benzene sulphonamide (L2), 4-((2-hydroxybenzylidene)amino-N-(pyridin-2-yl)benzene sulphonamide by the action of 2-hydroxybenzaldehyde with sulfathiazole/ sulfamethoxazole/ sulfapyridine in ethanolic media. **Methods:** The Schiff bases obtained were characterized by analytical data, IR, UV, ^{1}H- NMR, ^{13}C-NMR, Mass spectrum and monitored for cytotoxic activity against human breast cancer cell [MDA MB -231] line. **Findings:** The Schiff bases behaves as a bidentate ligand with oxygen and nitrogen as chelating positions and coordinates via phenolic oxygen and azomethine nitrogen. The composition of the ligands has been established by elemental analysis. Structural features and bonding mode of the Schiff bases have been proposed by spectral methods. The evaluated synthesized ligand shows excellent cytotoxic activity towards breast cancer cell line. **Novelty:** The evaluated highly biologically active L1 and L3 shows desirable cytotoxic activity towards [MDA MB -231] breast cancer cell line. The better IC_{50} value of the Schiff base ligands upgrades as chemotherapeutic agents which leads to drug formulation and induces DNA binding studies.

Keywords: 4-amino-N-(1; 3-thiazol-2-yl)benzenesulfonamide; 4-amino-N-(5-methyl-1; 2-oxazol-3-yl)-benzenesulfonamide; 4-amino-N-(pyridin-2-yl)benzenesulphonamide; 2-hydroxy benzaldehyde; cytotoxicity

1 Introduction

Schiff bases are versatile compounds which are synthesized by the condensation of amino compound with carbonyl compounds.[(1)] The Schiff base exhibit a broad range of biological activities like antibacterial, antifungal, antimalarial, antituberculosis, antipyretic, anti-inflammatory and antiviral properties.[(2–5)] The imine group from Schiff base has been shown to be critical towards biological activities.[(6)] Sulfa drugs possess SO_2NH moiety as an important toxophoric functions including antibacterial

and cytotoxic properties.[7–10] Sulphonamides as metabolites, compete with para–amino benzoic acid (PABA) for incorporation into folic acid.

Previously a number of biologically important Schiff bases have been reported by our group.[11–13] To broaden the scale of investigation on the Schiff bases, the present investigation records the synthesis followed by characterization of Schiff bases derived from sulpha drugs.

2 Materials and Methods

All chemicals and reagents used were of AR grade except ethanol which was purified prior to use. Solvents were purified and dried according to the standard procedures. Elemental analysis of the ligands was obtained using EL CHN rapid analyzer. IR spectra of the complexes were recorded as KBr pellets on a SHIMADZU 8000- FT IR spectrophotometer. The ^{13}C NMR and ^{1}H NMR spectra of the ligand was recorded with a Bruker Spectro spin advance (DPX-400) using TMS as internal standard and DMSO‑d6 as solvent. Melting points were determined by open capillary method (silicon bath electric melting point apparatus) and uncorrected. The electronic spectra of the ligands in UV –visible region was measured by using Perkin Elmer Lambda 35 spectrometer provided with quartz cells.

2.1 Synthesis of Schiff-Base ligands

To an ethanolic solution of 2-hydroxybenzaldehyde (0.01mole) an ethanolic solution of sulphamethoxazole /sulphathiazole/sulphapyridine (0.01mole) was added. The reaction mixture was refluxed for 4 to 5 hours. The coloured solid mass formed during refluxing was cooled, filtered, washed thoroughly with ethanol and dried a compound in a desiccator. The compound was recrystallisation from ethanol.

2.2 Cytotoxic evaluation

2.2.1 In Vitro cytotoxicity assay

The in vitro cytotoxicity of the newly synthesized ligands was carried out in human breast tumor cell lines. Cell line namely human breast cancer cell line [MDA MB -231] (NCL-Pune) was assayed by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) assay[14]. *In Vitro* cytotoxicity assay was carried out in the Laboratory of South India Textile Research Association (SITRA), Coimbatore, Tamil Nadu, INDIA.

2.2.2 Cell treatment procedure

The monolayer cells were detached with trypsin ethylene diamine tetra acetic acid (EDTA) to make single cell suspensions and viable cells were counted by trypan blue exclusion assay using a hemocytometry. The cell suspension was diluted with medium containing 5%FBS TO GIVE FINAL DENSITY OF $1X10^5$ cells/ml. one hundred microliters per well of cell suspensions were seeded into 96-wellplates at plating density of 10000 cells/well and incubated to allow for cell attachment at 370°C, 5%CO_2, 95% air and 100% relative humidity. After 24 hrs the cells were treated with serial concentrations of the test samples. They were initially dissolved in neat dimethyl sulfoxide (DMSO) and diluted to twice the desired final maximum test concentration with serum free medium. Additional four, serial dilutions were made to provide a total of five sample concentrations. Aliquots of 100μl of these different sample dilutions were added to the appropriate wells already containing 100μl of medium, resulted the required final sample concentrations. Following drug additional the plates were incubated for an additional 48 hrs at 370°C, 5%CO_2, 95% air and 100% relative humidity. The medium without samples were serving as control and triplicate was maintained for all concentrations.

2.2.3 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.[15,16] Therefore, the amount of formazan produced is directly proportional to the number of viable cells.

After 48hrs of incubation, 15μl of MIT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 370°C for 4 hrs. the medium with MIT was then flicked off and the formed formazan crystals were solubilized in 100μl of DMSO and then measured the absorbance at 570nm using micro plate reader.

The cytotoxic activity of the synthesized Schiff base were tested into five series of dilutions. The concentration of the compounds at percentage cell inhibition growth was calculated.

The percentage cell inhibition was determined using the formula.

% Cell inhibition = 100- Abs (sample) / Abs (control) X 100 [17]

Nonlinear regression graph was plotted between %cell inhibition and log concentration and IC_{50} was determined using graph pad prism software.

3 Results and Discussion

In the present work, the Schiff base are 4-((2-hydroxybenzylidene)-amino-N-(5-methyl-1,2-oxazol-3-yl) benzene sulphonamide (L1),4-((2-hydroxybenzylidene)-amino-N-(pyrindin-2-yl)benzene sulphonamide (L2), 4-((2-hydroxybenzylidene)-amino-N-(1,3-thiazol-2-yl)benzene sulphonamide (L3) has been synthesized. The stoichiometry of the compounds has been determined by standard procedures.

The ligands were characterized by

- Analytical data- colour, melting point, elemental analysis.
- Infrared spectra
- Electronic spectra
- ^{1}H-NMR spectra
- ^{13}C-NMR spectra
- EI –MASS spectra

3.1 Analytical data

The analytical data and physical characteristics of the Schiff base ligands are indicated in the Table 1 .

Table 1. Physical characteristics and analytical data of Schiff base ligands

Sl. No	Schiff base	Molecular formula	Colour	Yield %	Melting Point ^{0}C	Elemental analysis % found (calcd)			
						C	H	N	S
1	L_1	$C_{18}H_{16}N_3O_4S$	Orange	85	202	57.79 (58.37)	4.21 (4.32)	10.92 (11.31)	8.52 (8.64)
2	L_2	$C_{19}H_{17}N_3O_4S$	Red orange	80	180	59.38 (59.48)	4.42 (4.01)	10.93 (10.94)	8.33 (8.82)
3	L_3	$C_{16}H_{13}N_3O_3S_2$	Yellow	80	270	52.93 (53.48)	3.30 (3.62)	10.81 (11.69)	17.45 (17.82)

3.2 IR Spectrum

The ligands used in the present investigation contains five donor sites

1. phenolic oxygen
2. azomethine nitrogen
3. sulfonamide oxygen
4. sulfonamide nitrogen
5. ring nitrogen

The vibrational spectra of the ligands shows a band in the region of 1616 cm^{-1}– 1627cm^{-1} corresponds to $\nu_{(>c=N-)}$ group[18] and another broad band between 3418 cm^{-1} –3471 cm^{-1} which is the characteristic frequency of hydrogen bonded phenolic $\nu_{(O-H)}$ stretching vibration [18,19].

$$Schiff\ base\ L1\ IR\ (solid\ state,\ cm^{-1}):\ 1616\ v(>C=N-);\ 3471\ v(O-H);\ 1406\ vas(SO_2);\ 2934\ vs(SO_2)\ ;\ 2963\ v(N-H)$$

$$Schiff\ base\ L2\ IR\ (solid\ state,\ cm^{-1}):\ 1627\ v(>C=N-);\ 3418v(O-H);\ 1384\ vas(SO_2);\ 2927\ vs(SO_2)\ ;\ 2972\ v_{(N-H)}$$

$$Schiff\ base\ L3\ IR\ (solid\ state,\ cm^{-1}):\ 1616\ v(>C=N-);\ 3462\ v(O-H);\ 1417\ \ vas(SO2);\ 2919\ vs(SO2)\ ;\ 2938\ v_{(N-H)}$$

3.3 Electronic spectra

The electronic spectra of the ligands show two absorption maxima corresponds to л-л* and n-л* transitions due to azomethine linkage and aromatic parts of the ligands.[17,20]

$$L1\ (\lambda\ max\ nm\ (cm^{-1}):\ 277\ nm\ (36101\ cm^{-1})\ \pi-\pi*\ transition$$
$$344nm\ (29069\ cm^{-1})\ n-\pi*\ transition\ (azomethine\ linkage)$$
$$L2(\lambda\ max\ nm(cm^{-1}):213\ nm(43202\ cm^{-1})\pi-\pi*(aromatic\ part\ of\ the\ ligand)$$
$$218\ nm\ (41389\ cm^{-1})\ n-\pi*\ transition$$
$$L3\ (\lambda\ max\ nm\ (cm^{-1}):\ 279\ nm\ (35842\ cm^{-1})\ \pi-\pi*\ transition$$
$$345nm\ (28985\ cm^{-1})\ n-\pi*\ transition$$

3.4 ^{1}H-NMR spectrum

The proton magnetic resonance spectrum of the Schiff bases was taken in DMSO –d_6 solvent was shown in Figures 1, 2 and 3

$^1H-NMRL_1$:	8.94ppm(1H)(S)	$-CH=N-$
$(DMSO-d_6ppm)$	12.47ppm(1H)(S)	$-OH$
	6.57 – 7.91ppm	aromatic protons
	6.98 – 7.70ppm(4H)	- N-phenyl
	7.47ppm(d)(2H)	-oxazolemoiety [23]

$^1H-NMRL2$:	1*l*3.81ppm(3H)	$-OCH_3$
$(DMSO-d_6ppm)$	1*c*6.87 – 7.24ppm(3H)(m)	phenolic ring
	7.51 – 8.00ppm(m)(4H)	pyridine ring
	7.71 – 7.75ppm(m)(4H)	$-N-$ phenyl
	8.94ppm	$-CH=N-$

^{1} H-NMR L3:	8.96ppm(1H)(S)	$-CH=N-$
$(DMSO-d_6ppm)$	12.61ppm(1H)(S)	$-OH$
	6.58 – 7.88ppm	aromatic protons
	7.40 – 7.42ppm	thiazole moiety

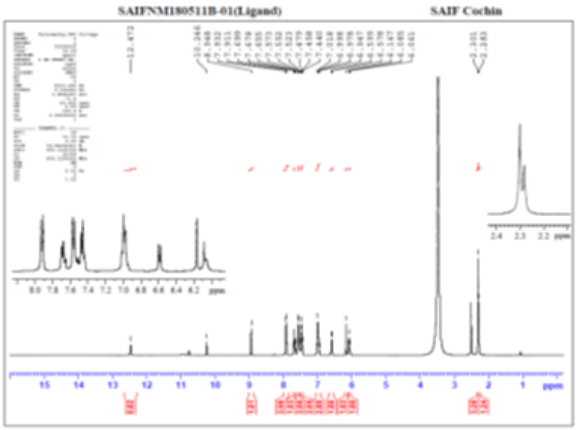

Fig 1. ^{1}H NMR spectrum

4-((2-hydroxybenzylidene)-amino-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide (L1)

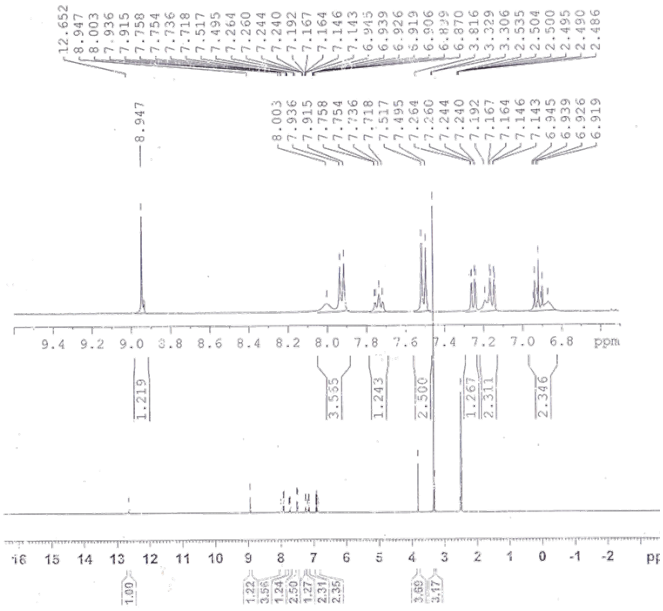

Fig 2. ^{1}H NMR spectrum

4-((2-hydroxybenzylidene)amino-N-(pyridin-2-yl)benzenesulfonamide (L2)

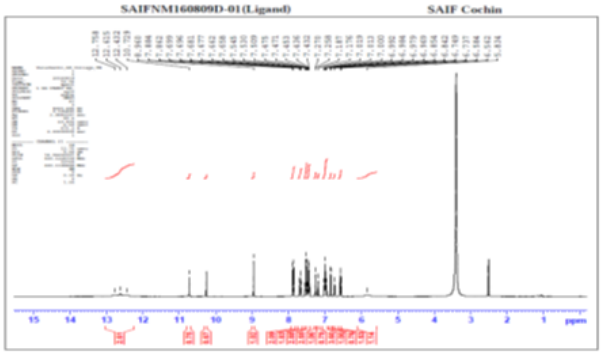

Fig 3. ^{1}H NMR spectrum

4-((2-hydroxybenzylidene)amino-N-(1,3-thiazol-2-yl)benzenesulfonamide (L3)

3.5 ^{13}C-NMR spectrum

The ^{13}C-NMR spectrum of the Schiff bases was taken in DMSO –d_6 solvent

$^{13}C-MMR$ spectrum L1: 165.4ppm$(-CH=N-)$
7.47ppm$(d, 2H,$ oxazole moiety)
160.6(phenolic C-OH)
128.2, 112.5, 152.6 $(C_1, C_2, C_3 - N$-phenyl)
136.8, 132.5, 122.1, 119.1, 117.1 $(C_1, C_2, C_3, C_4, C_5$ - phenolic ring)[24].

^{13}C-NMR spectrum L2: 150.6 (phenolic C-OH)
148.2, 117.5, 138.6&112.0 (C_1, C_2, C_3, C_4 pyridine ring)
138.6 (C_1 N-phenyl)
128.8 (C_2C_6 N-phenyl)
153.2 (C_4 N-phenyl)
119.1, 123.7, 115.9, 150 ($C_1, C_2, C_3, C_4, C_5, C_6$ phenolic ring)

$^{13}C-NMR$ spectrum L3: $165.1ppm(-CH=N-)$
$150.6($ phenolic $C-OH)$
$168.8, 112.4, 147.9$ (C_1, C_2, C_4-thiazole)
$122.4, 127.6, 147.9$ ($C_2\&C_6, C_3\&C_5, C_4,$ N-phenyl)
$119.1, 124.4, 116$ ($C_1, C_2.C_3\&C_4,$ phenolic ring)

3.6 Mass Spectrum

The mass spectral data of the ligand is consistent with the formulation corresponds to [M+3] and M peaks respectively shown in (Figures 7 and 8)

$$\text{Ligand} - 1C_{18}H_{16}N_3O_4S : m/z = 357 \text{ (calcd., 357)}$$

$$\text{Ligand-2 } C_{19}H_{17}N_3O_4S : m/z = 384.20(\text{ calcd., } 384.00)$$

$$\text{Ligand} - 3C_{16}H_{13}N_3O_3S_2 : m/Z = 363.229(\text{ calcd. } 359)$$

Based on the above spectral studies the following structure is proposed for the Schiff bases,

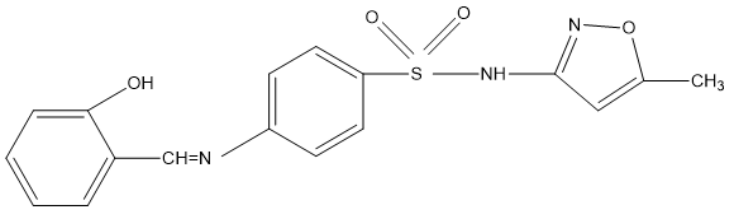

Fig 4. Structure of Schiff base ligand(L1)

4-[(2-hydroxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl) benzene sulphonamide (L1)

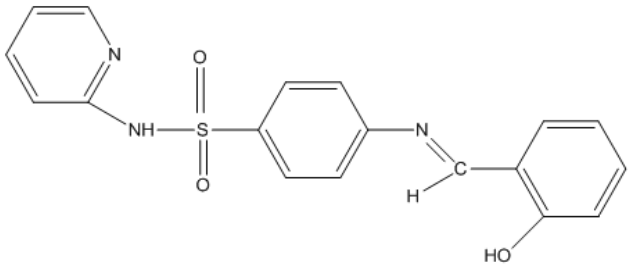

Fig 5. Structure of Schiff base ligand (L2)

4-((2-hydroxy benzylidene)-amin -N-(pyridin-2-yl) benzene sulphonamide (L2)

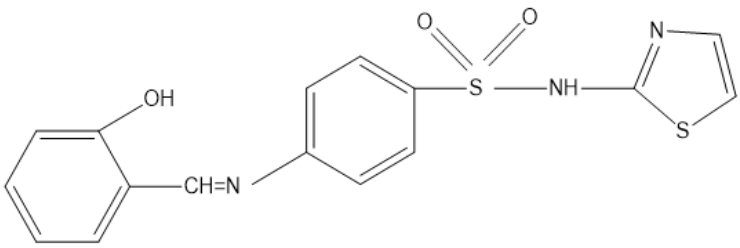

Fig 6. Structure of Schiff base ligand (L3)

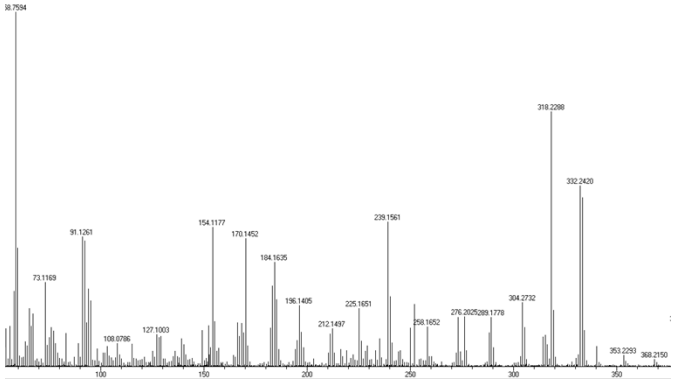

Fig 7. Mass spectrum4-((2-hydroxybenzylidene) amino-N-(1, 3-thiazol-2-yl) benzenes ulphonamide (L3)

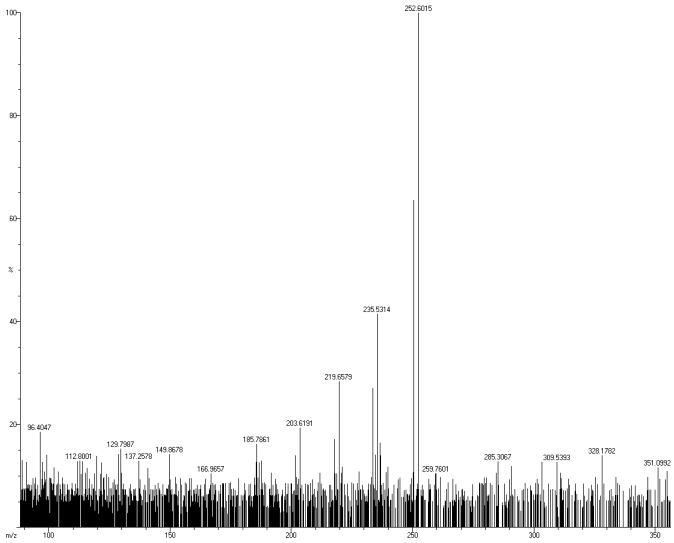

Fig 8. Mass spectrum of 4-((2-hydroxybenzylidene)-amino-N-(5-methyl-1.2-oxazol-3-yl)benzene sulfonamide (L1)

3.7 Cytotoxic Activity

The cytotoxic activity of the synthesized ligands is shown in the Figures 9, 10 and 11. Tables 2, 3 and 4

- The ligand 4-((2-hydroxy benzylidene)-amino-N- (5-methyl-1,2-oxazol -3-yl) benzene sulphonamide (L1) and 4-((2-hydroxybenzylidene)-amino-N-(1,3-thiazol-2-yl)benzene sulphonamide (L3) shows excellent cytotoxicity towards human breast cancer cell[MBA MB-231].
- The ligand 4-((2-hydroxybenzylidene) amino-N-(pyridin-2-yl)benzene sulphonamide (L3) Show moderate cytotoxicity towards human breast cancer cell [MDA MB-231].
- The order of activity
  Ligand(L1) =Ligand (L3)> ligand (L2)

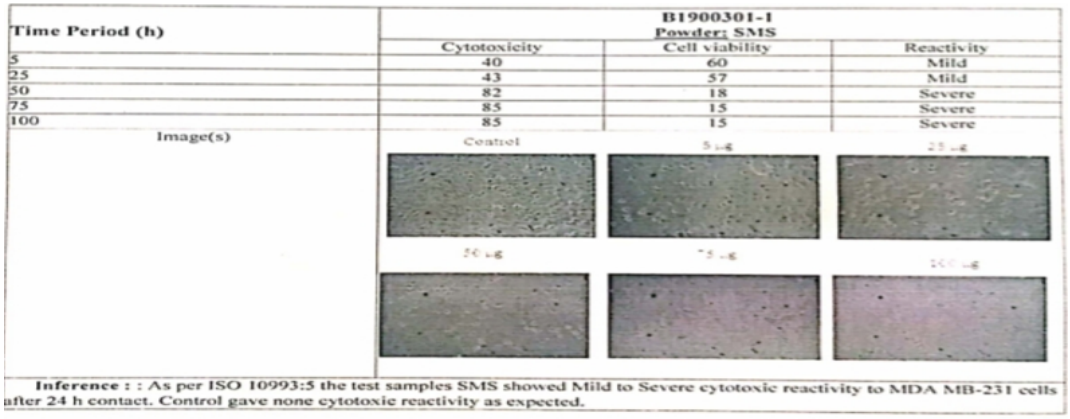

Fig 9. In vitro cytotoxic assay of L1 against [MDA MB-231]

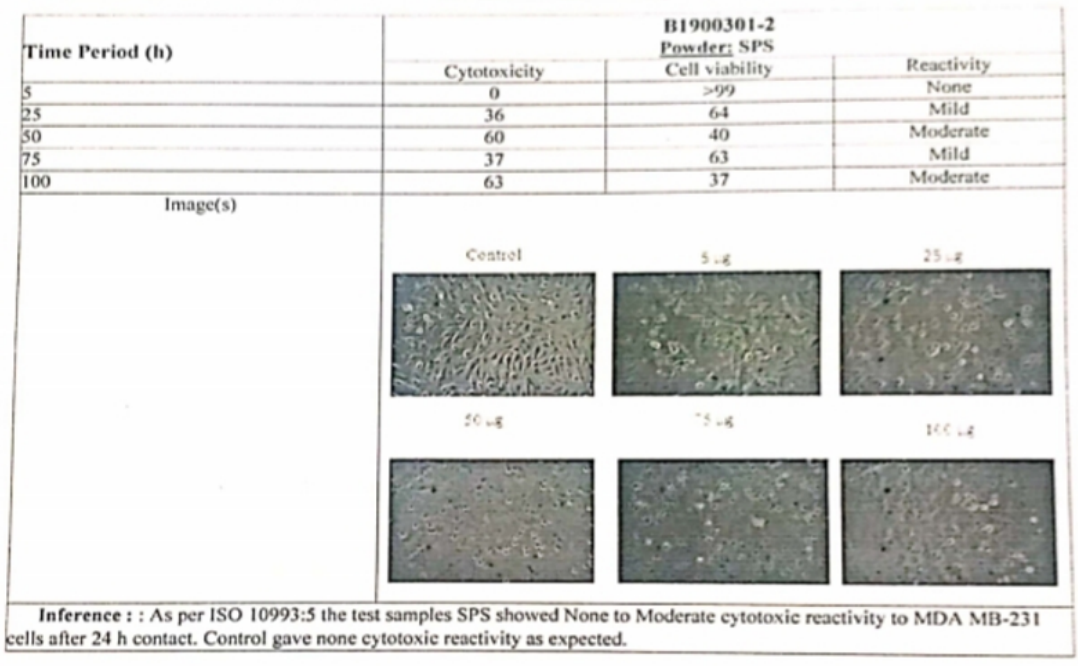

Fig 10. In vitro cytotoxic assay of L2 against [MDA MB-231]

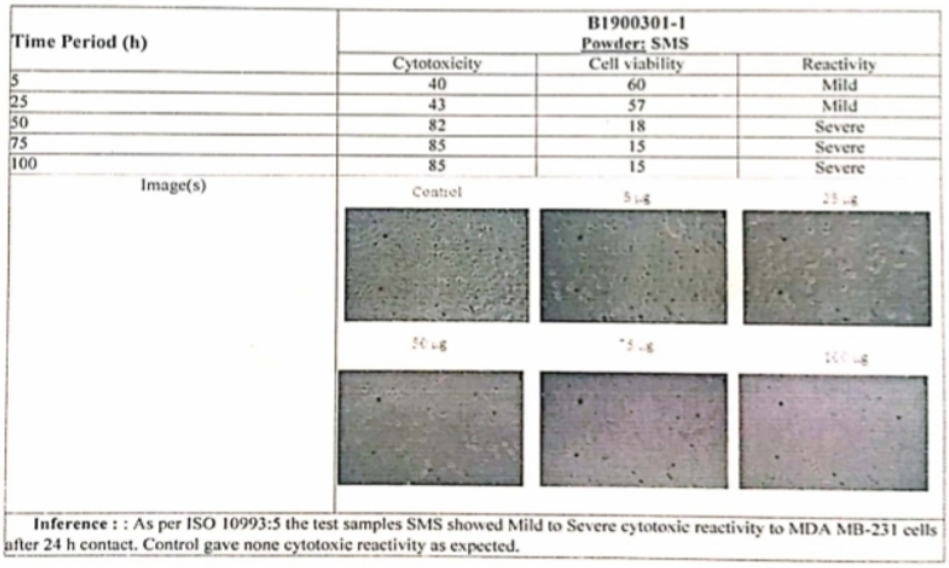

Fig 11. In vitro cytotoxic assay of L3 against [MDA MB-231]

Table 2. In Vitro cytotoxicity assay of L1 against [MDA MB -231]

Concentration(μm)	% Cell inhibition
5	40
25	43
50	82
75	85
100	85

Table 3. In Vitro cytotoxicity assay of L2 against [MDA MB -231]

Concentration (μm)	% Cell inhibition
5	0
25	36
50	60
75	37
100	63

Table 4. In Vitro cytotoxicity assay of L3 against [MDA MB -231]

Concentration(μm)	% Cell inhibition
5	0
25	61
50	82
75	87
100	80

The predominant activity of the ligands derived from L1 and L3 may be accounted for in terms of the presences of oxazole and thiazole units in the synthesized ligands. The concentration of the complex at 50% cell growth was inhibited and IC_{50} was calculated as shown in Table 4.

4 Conclusion

The bidentate coordination ability of the newly synthesized azo Schiff bases was proved by IR, UV, NMR and mass spectra which confirms two donor sites: azomethine nitrogen and phenolic oxygen. The synthesized Schiff bases were subjected to anticancer activity against human breast cancer cell [MDA MB -231] line. The order of activity is Ligand(L1) =Ligand (L3)> ligand (L2). The predominant activity of the ligands derived from L1 and L3 is due to the presence of oxazole and thiazole units in the synthesized ligands. The better IC_{50} cytotoxic activity of the ligands against breast cancer cell [MDA MB-231] line may pose a significant role in metallodrug formulation in the field of bioinorganic chemistry. The biological activity of the Schiff bases was enhanced by complexation with metal ions.

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