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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF THREE NEW SCHIFF BASES DERIVED FROM AMINO ACIDS AND THEIR Ag(I) COMPLEXES

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ABSTRACT. Three Schiff base ligands which were derived from glycine, asparagine and alanine L^1, L^2 and L^3 were designed and used to synthesized their Ag(I) complexes. ^{1}H NMR, FT-IR, UV-Visible and conductance techniques were used to characterize the ligands and their metal complexes. The synthesized compounds showed antioxidant activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH). Schiff bases and their Ag(I) complexes were screened for antimicrobial activity, in vitro antibacterial activity against three gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhi* with two gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* by micro plate almar blue assay (MABA), antifungal activity against *Candida albicans* and *Candida glabrata* by agar tube dilution protocol. In vitro anti-inflammatory activity was performed by heat induce denaturation method and in vivo anti-inflammatory activity was performed by induced paw edema method. Cytotoxicity of the synthesized compounds was recorded against cyclohexamide by MTT assay. Ag(I) metal complexes showed more significant biological activities as compared to ligands.

KEY WORDS: Schiff bases, Metal complexes, Cytotoxicity, Antifungal, Antibacterial, Anti-inflammatory

INTRODUCTION

Schiff bases are important category of compounds which could serve as functional models for the elucidation of structures of biomolecules and biological processes. They are often used as important ligands especially the ones bearing N, O, S donor atoms which exhibit structural similarities with neutral biological systems [1]. One of their structural significance has been the inherent interpretation of the mechanism of transformation of racemization reaction in biological systems attributed to the imine group (C=N). They also serve as one of the most relevant synthetic ligand systems, with importance in asymmetric catalysis, conducting materials and polymers, crystal engineering and therapeutic agents. Schiff bases have proven to be cheap starting precursors with relatively easy synthetic route [2]. The high purity, low toxicity, and eco-friendliness have made the synthesis and structural studies of new Schiff base compounds very interesting.

It is well known that Schiff base derivatives have received a great deal of attention because of their easy synthetic procedures and widely applications in organic electronics and chemical sensors [3]. In particular, salicylaldimine derivatives, as a kind of important Schiff bases, often exhibited special properties, such as tunable fluorescence, photochromism, thermochromism, solvatochromism, liquid crystal and nonlinear optical properties [4].

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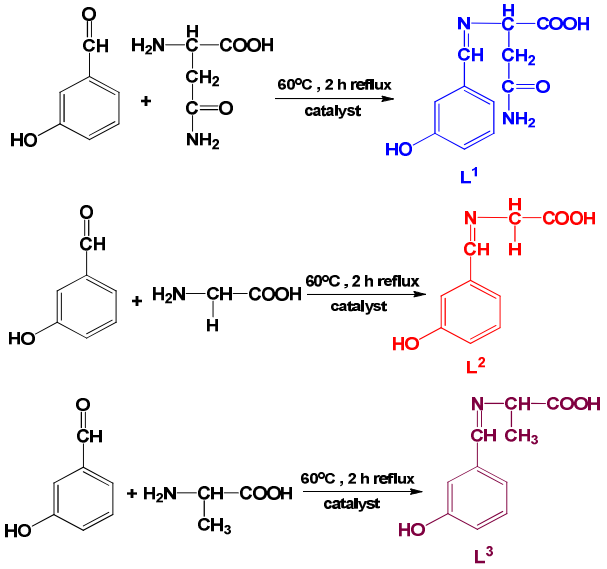
Imines starting from glycine and benzaldehyde were previously synthesized [5-7]. Availability of one lone pair of electrons on N-atom makes imines very important in biological systems [8]. Imines derived from amino acids are very stable [9] and these are easily soluble in organic solvents at room temperature [10]. Schiff bases are one of the most widely used organic compounds and unveil a broad array of biological activities including antifungal, antibacterial, antiproliferative, antimalarial and antipyretic. Imine group also appears in many natural products those are very important for their biological activity. Other commercial applications of Schiff bases like herbicidal, plant growth regulator, polymer, catalyst, dyes, and anti-corrosive [11-16]. A large number of the world's community deceased due to cancer every year. Schiff bases served as effective anti-cancerous agents due to reactivity of imine group [17]. Schiff bases with high levels of N and O molecules which can affect DNA nitrogenous bases and cell structure leading to mutation and hence can be used to cure cancer [18]. Amino acid based Schiff bases form very stable metal complexes because of imine group (C=N) [19]. Schiff base derived from amino acid act as bioactive molecule [20].

These kind of bases also have variety of applications in the modern technologies as in optical devices such as computers, in imaging processes, photodetectors and non-linear optical materials [21] and they may also serve as stationary phases in spectroscopic instruments due to their thermal stability at high temperature [22, 23]. There are many methods to combine transition metals to organic compounds in which Schiff bases showed many reactions with transition metals [24, 25]. Transition metal complexes of Schiff bases also play important role in coordination chemistry [26]. Schiff base transition metal complexes are used as catalysts in inorganic redox chemistry and electrochemical reactions as dyes, pigments, fluorescent material and biomedicine [27]. Metal chelated complexes have redox active central metal atom due to presence of metal complexes shows more application than simple organic ligands [28]. Drugs become more effective when chelated with transition metal like metal complexes of Schiff base phenolate is used for the treatment of cancer [29]. Schiff base transition metal complexes show high stability against heating and oxidation as compared to ligand [30].



Scheme 1. Synthesis and the chemical structures of L^1, L^2 and L^3.

By keeping these ideas in our mind, in this article, we explore the analogy study of different three new Schiff base ligands which were derived from glycine, asparagine and alanine with 3-hydroxybenzaldehyde (Scheme 1). Moreover, their Ag(I) metal complexes were synthesized and structural characterization was done by using ^{1}H NMR, FT-IR, UV-vis and conductance techniques. Synthesized compounds were tested for antimicrobial, cytotoxicity, antioxidant and anti-inflammatory activities, to evaluate their activeness against standard drugs.

EXPERIMENTAL

Chemicals

Glycine, alanine, asparagine and 3-hydroxybenzaldehyde were purchased from Sigma Aldrich. Carboxymethyl cellulose (CMC) and carrageenan were obtained from Fluka Chemical. The solubilities of the synthesized compounds were tested in organic solvents. Metrohm 644 conductometer, Boethius apparatus, Perkin Elmer 1650 spectrophotometer, Advance NEO 400 MHz and 6000 PC UV-Vis spectrophotometer were used to find conductance, melting point, FT-IR, ^{1}H-NMR and UV spectra, respectively.

Synthesis of L^1

Ligand **L^1** were synthesized by mixing hot aqueous solutions of 1 mmol of alanine, asparagine and glycine (0.132, 0.075 and 0.089 g), respectively, with hot ethanolic solution of 3-hydroxybenzaldehyde (0.122 g, 1 mmol). The reaction mixture was subsequently heated at 60 ^{o}C for 2 hours, in the presence of 2-3 drops of hydrated dimethylamine as catalyst. After completion of the reaction time, the aqueous ethanolic solution was left to slowly evaporate at room temperature. After 16 hours, crystals were obtained. These were washed with cold ethanol and ethyl ether, and dried it in vacuum oven at 60 ^{o}C temperature and 1 atm pressure. Molecular formula: $C_{10}H_{11}NO_3$; orange solid; yield 65%; m.p.: 135 ^{o}C; molecular weight: 193.20 g/mol; IR (cm^{-1}): 1667 (C=N), 1280 (OH)-phenol, 1577 (C=C), 3188 (C-H) benzene, 1735 (C=O), 3527 (O-H); ^{1}H NMR [(400 MHz, DMSO-d_6, δ ppm), *J*(Hz)]: δ 12.80 (d, 4.2, 3H, H-2, H-6, H-2', H-6'); 12.97 (s, 2H, H-11, H-9'); anal. calc., (%) for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25; O, 24.84.

Synthesis of L^2

Ligand **L^2** were synthesized as **L^1**. Molecular formula: $C_{11}H_{12}N_2O_4$; orange brown solid; yield 71%; m.p.: 112 ^{o}C; molecular weight: 236.22 g/mol; IR (cm^{-1}): 1683 (C=N), 1282 (OH)-phenol, 1578 (C=C), 3196 (C-H) benzene, 1617 (C=O), 3520 (O-H); ^{1}H NMR [(400 MHz, DMSO-d_6, δ ppm), *J*(Hz)]: δ 11.70 (d, 5.3, 4H, H-2, H-5, H-2', H-5'); 10.87 (s, 2H, H-10, H-10'); anal. calc., (%) for $C_{11}H_{12}N_2O_4$: C, 57.36; H, 6.02; N, 11.15; O, 25.47.

Synthesis of L^3

Ligand **L^3** was synthesized as **L^1**. Molecular formula: $C_9H_9NO_3$; yellow solid; yield 70%; m.p.: 123 ^{o}C; molecular weight: 179.17 g/mol; IR (cm^{-1}): 1668 (C=N), 1244 (OH)-phenol, 1579 (C=C), 3191 (C-H) benzene, 1457 (C=O), 3535 (O-H); ^{1}H NMR [(400 MHz, DMSO-d_6, δ ppm), *J*(Hz)]: δ 10.70 (d, 5.2, 3H, H-2, H-4, H-2', H-4'); 11.90 (s, 2H, H-9, H-11'); anal. calc., (%) for $C_9H_9NO_3$: C, 61.84; H, 6.23; N, 7.21; O, 24.71.

Synthesis of Ag-L^1 complex

The newly synthesized Schiff base (1 mmol, 0.193 g **L^1**, 0.236 g **L^2**, 0.179 g **L^3**, respectively) were dissolved in 10 mL hot ethanol, for 20 min at 60 ^{o}C, and subsequently mixed a solution of $AgNO_3$ (1 mmol, 0.169 g) in 10 mL of ethanol; 2 mL of water and a few drops of acetic acid were

then added to the reaction mixture which was heated for 3-4 hours at 60 ºC. After cooling the reaction mixture was kept for 48 hours at room temperature to allow the formation of sharp needle like crystals. These were washed with ethanol and ethyl ether to remove solvent and impurities, and let to dry in an oven at 60 ºC and 1.01325 bar pressure. Molecular formula: $C_{10}H_{10}AgNO_3$; white solid; yield 75%; m.p.: 186 ºC; molecular weight: 300.6 g/mol; IR (cm^{-1}): 1664 (C=N), 1243 (OH)-phenol, 1490 (C=C), 3192 (C-H) benzene, 1617 (C=O), 3560 (O-H), 451 (M-N); (Figure 1).

$$L^1 + AgNO_3 \rightarrow [Ag\text{-}L^1] + HNO_3 \quad (1)$$

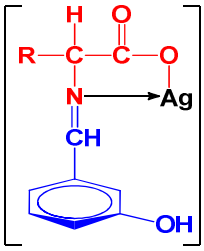


Figure 1. Proposed structure of metal complexes (where R = R', R", R'"; R' = CH_3- (alanine), R" = $NH_2CO\text{-}CH_2$- (asparagine), R'" = H- (glycine).

Synthesis of Ag-L^2

Complex [Ag-L^2] were synthesized as **[**Ag-L^1]. Molecular formula: $C_{11}H_{11}AgN_2O_4$; brown solid; yield 60%; m.p.: 155 ºC; molecular weight: 343.08 g/mol; IR (cm^{-1}): 1669 (C=N), 1279 (OH)-phenol, 1354 (C=C), 3198 (C-H) benzene, 1438 (C=O), 3550 (O-H), 460 (M-N).

$$L^2 + AgNO_3 \rightarrow [Ag\text{-}L^2] + HNO_3 \quad (2)$$

Synthesis of Ag-L^3

Complex [Ag-L^3] were synthesized as **[**Ag-L^1]. Molecular formula: $C_9H_8AgNO_3$; grayish black solid; yield 79%; m.p.: 195ºC; molecular weight: 286.03 g/mol; IR (cm^{-1}): 1666 (C=N), 1153 (OH)-phenol, 1560 (C=C), 3201 (C-H) benzene, 1356 (C=O), 3552 (O-H), 462 (M-N).

$$L^3 + AgNO_3 \rightarrow [Ag\text{-}L^3] + HNO_3 \quad (3)$$

RESULTS AND DISCUSSION

FT-IR

FT-IR graph was noted at 400-4000 cm^{-1} for synthesized compounds. Ligands and metal complexes were compared and confirmed the presence of -CH=N- (imine) in ligands appeared at 1667, 1683 and 1668 cm^{-1} for L^1, L^2 and L^3, respectively in (Table 1). Some of peaks are appeared at 3500-2000 cm^{-1} in amino acids were not present in the spectra of ligands similarly peaks for carbonyl group (aldehyde) showed at 1720 cm^{-1}which is not showing the complete formation of Schiff bases. The FT-IR spectra predicted all the absorption bands of the Schiff base ligands and some new bands at specific frequency confirmed the modes of absorption and the coordination of the ligands (L^1, L^2 and L^3) with the Ag metal ions through azomethine nitrogen and oxygen. Decrease in band characteristics for 1664, 1669 and 1666 cm^{-1} as compared to ligand peaks

confirmed the formation of complexation with silver metal. In the spectra of metal complexes weak band appeared at (466-434 cm^{-1}) confirmed the metal to ligand bond. The OH bond of carboxylic acid disappeared in the IR spectra of metal complexes confirmed that oxygen involved in chelating process. M-O weak band appeared at (440-420 cm^{-1}) [31].

Table 1. FT-IR data of compounds.

Compounds	ν(C=N)	ν(M-N)	ν(M-O)	ν(C=C)	ν(C=O)	ν(O-H)
L^1	1667	-	-	1577	1735	3527
[Ag-L^1]	1664	451	420	1490	1617	-
L^2	1683	-	-	1578	1617	3535
[Ag-L^2]	1669	460	432	1354	1438	-
L^3	1668	-	-	1579	1457	3550
[Ag-L^3]	1666	462	440	1560	1356	-

^1H NMR

^1H NMR spectra of three new Schiff base ligands (L^1, L^2 and L^3) was recorded in the presence of DMSO-d_6 solvent [32]. Peaks were detailed on Bruker 300 MHz instrument. ^1H NMR spectrum of the Schiff base ligand showed the peak at around δ 12.80 ppm is attributed to the OH-proton of carboxylic acid. As well as, we could observe that there was only one singlet peak observed at δ 12.97 ppm. The imines protons in aromatic benzene ring protons were shown in the form of multiplet at δ 7.562 - 6.743 ppm, one more de-shielded singlet was recorded at δ 8.404 ppm for (-CH=N-) proton, one singlet was observed at δ 9.890 ppm for OH group. In the mean time, the peaks attributed to the aromatic protons had similar variation trend.

UV-visible spectroscopy

Spectrum for synthesized new compounds was recorded in alcoholic environment. λ_{max} values for ligands were in the range of 350-345 nm which reveals metal to ligand charge transfer, predicted π-π* transition for imine group (-CH=N-). λ_{max} values from 325-335 nm shows complexation (Table 2) [33].

Molar conductance

The conductance of synthesized compounds was measured by making 10^{-3} M molar solution in DMSO at 27 ºC by conductometer. Values of the measured molar conductance were in the range of 12–30 $\Omega^{-1}.cm^2.mol^{-1}$. The given data revealed that ligands and their Ag(I) complexes were non-electrolyte in nature [34] (Table 2).

Table 2. Analytical data and physical properties of the synthesized compounds.

Compound	Formula	M.p. (ºC)	λ_{max} (nm)	Found (Calculated) C	H	N	Ag	Conductance ($\Omega^{-1}.cm^2.mol^{-1}$)
L^1	$C_{10}H_{11}NO_3$	135	350	62.00 (62.17)	7.68 (5.74)	7.19 (7.25)	-	15.65
[Ag-L^1]	$C_{10}H_{10}AgNO_3$	186	325	40.00 (40.03)	3.30 (3.36)	4.61 (4.67)	35.90 (35.95)	26.78
L^2	$C_{11}H_{12}N_2O_4$	112	340	57.25 (57.36)	6.06 (6.12)	11.10 (11.15)	-	14.12
[Ag-L^2]	$C_{11}H_{11}AgN_2O_4$	155	330	38.42 (38.51)	3.17 (3.23)	8.13 (8.17)	31.39 (31.44)	26.45
L^3	$C_9H_9NO_3$	123	345	61.72 (61.84)	6.14 (6.20)	7.19 (7.21)	-	12.67
[Ag-L^3]	$C_9H_8AgNO_3$	195	335	37.21 (37.39)	2.76 (2.82)	4.84 (4.90)	37.65 (37.71)	30.30

Cytotoxicity (MTT Assay on 3T3 Cells)

3T3 fast growing primary mouse embryonic fibroblast cells were used for cytotoxicity assay, initially these dissolved in DMSO to get required amount of cells for the assay. 0.5 mg of each synthesized compound was screened for cytotoxicity against standard drug Cyclohexamide. Drug was added on plates and incubated at 37 ºC for 48 hours. MTT dye was added on plates and further incubated for 4-5 hours. Percentage cell inhibition and IC_{50} values were measured for the compounds as well as it shows in (Figure 2). All metal complexes show significant activity rather than ligands [35, 36].

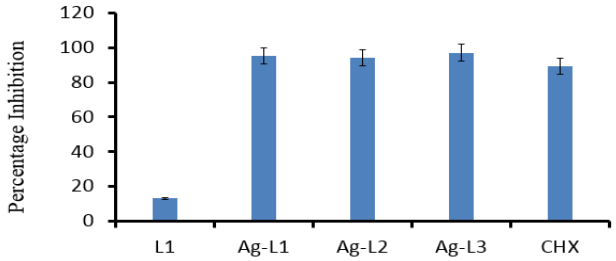


Figure 2. Cytotoxicity results of compounds.

Antibacterial

In vitro, antibacterial activity was done by microplate alamar blue assay (MABA) against *Staphylococcus aureus (+)*, *Bacillus subtilis (+)* and *Escherichia coli (—)*, *Pseudomonas aeruginosa (—)*, *Salmonella typhi (—)* bacterial species. Streptomycin (stm) served as standard antibacterial drug (Figure 3) [37].

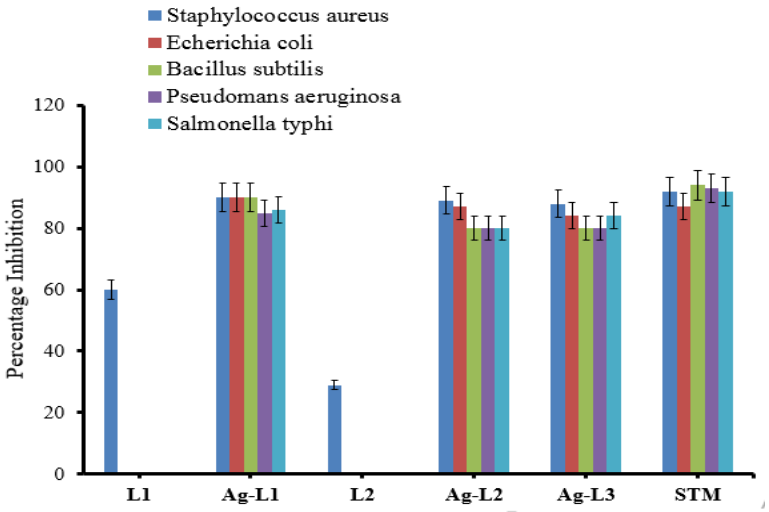


Figure 3. Antibacterial activity

Antibacterial activity of synthesized compounds was done by taking 200 µg/mL of sample against 200 µg/mL of Streptomycin as standard by the Microplate Alamar Blue Assay (MABA).

Antifungal

In vitro, antifungal bioassay was done by agar tube dilution protocol against *Candida albicans* and *Candida glabarats* fungus using Miconazole as standard drug to find out reactiveness of ligands and metal complexes against commercially available standard. Sample compounds were taken 200 µg/mL in DMSO solution and heated at 27 ºC for 1 week on 96 well tubes (Figure 4) [38].

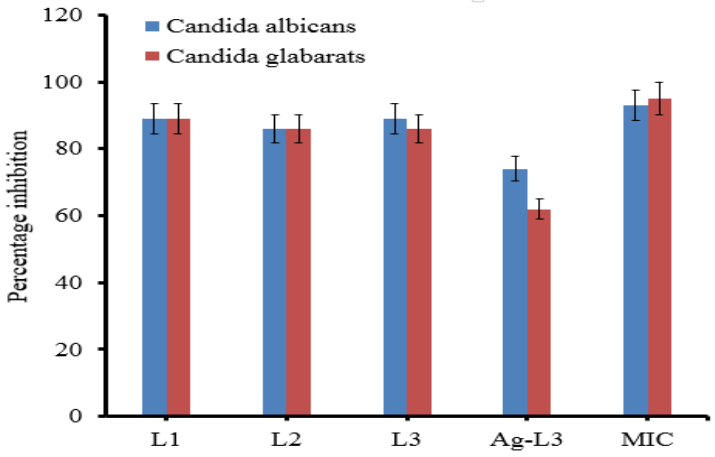


Figure 4. Antifungal activity

Antifungal activity was screened by taking 200 µg/mL of synthesized compounds against Miconazole µg/mL used as standard by Agar tube dilution protocol.

Anti-inflammatory

In-vitro heat induced protein denaturation method

Fresh egg albumin was taken and made ethanolic solution of the 0.004 g of the synthesized compounds and further made dilutions of about 400, 200, 100, 50 and 25 µg/mL. PBS (phosphate buffered saline) solution pH was maintained up to 6.4 by adding 1-2 drops of 1 M HCl. 1 M Diclofenac sodium solution serve as standard. Added 0.2 mL of the egg albumin in each bottle by micro pipette, 2.8 mL of the PBS solution and 2 mL of sample solution as test compound; 2 mL of the ethanol, 0.2 mL of egg albumin and 2.8 mL of PBS solution used as control solution. Incubated all samples at 37 ºC for about 15 min and then for 5 more min at 60 ºC temperature [39] (Figure 5). Calculated percentage inhibition of the sample and standard by the formula:
Percentage inhibition of protein denaturation = $(1 - V_t/V_c) \times 100$, where V_t = absorbance of test sample, V_c = absorbance of control.

In-vivo assay

Animals

Albino rats (of weight 200-250 g each) were housed and fed under standard laboratory condition according to the animal ethical committee of Institute of Chemistry, Punjab University, Pakistan [40].

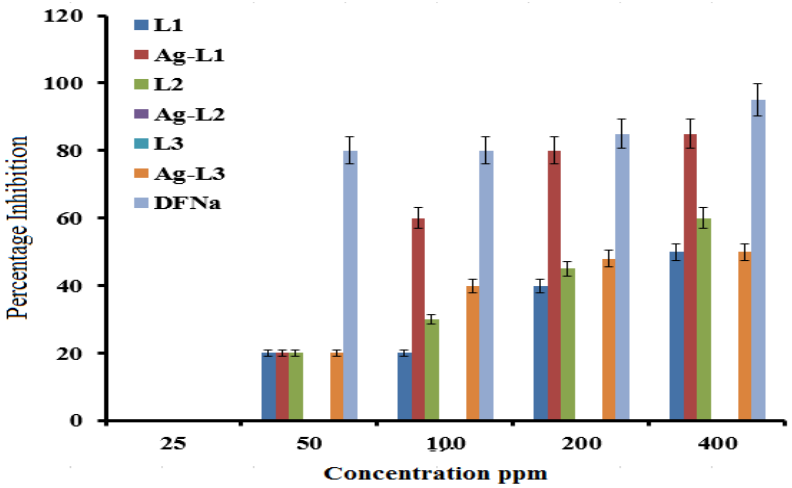


Figure 5. Percentage inhibition results of synthesized compounds.

Paw edema method

Rats were taken in 3 groups including test group, standard and control. Group 1 (test) was given orally 100 µL of synthesized drug in 1% CMC solution. Group 2 (standard) receives 1.0 mg diclofenac sodium by gauge. Group 3 (control) was given 100 µL of distilled water. After 30 min of oral administration of related drug to all groups about Carrageenan (0.1 mL) injected on the right hind paw [41]. All paws were marked in such a way that every time we get accurate volume with minimum chances of error. Paw volume was noted from 0-4 hours to get series of reading showing level of inflammation. Percentage inhabitation [42] was recorded by using following equation: Percentage inhibition = $(1 - V_t/V_c) \times 100$, where V_t refers to increase in paw volume of test drug and V_c is for control (Figure 6) and Paw volume (Figure 7).

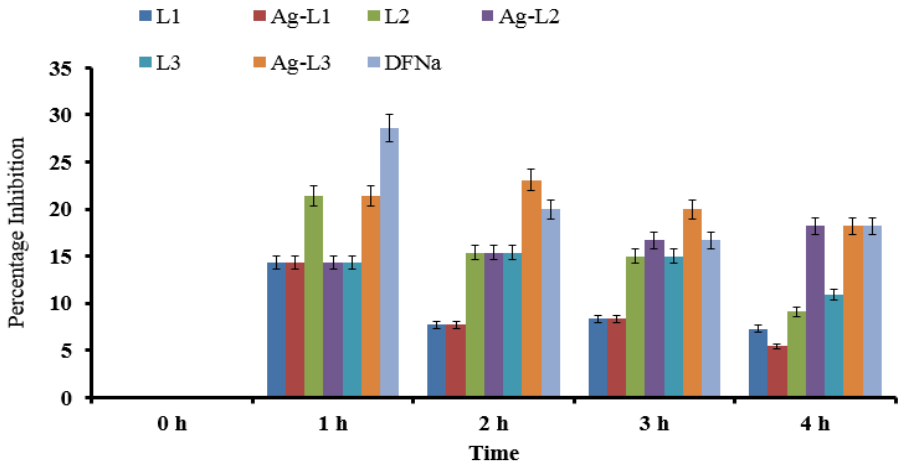


Figure 6. Percentage inhibition of the compounds.

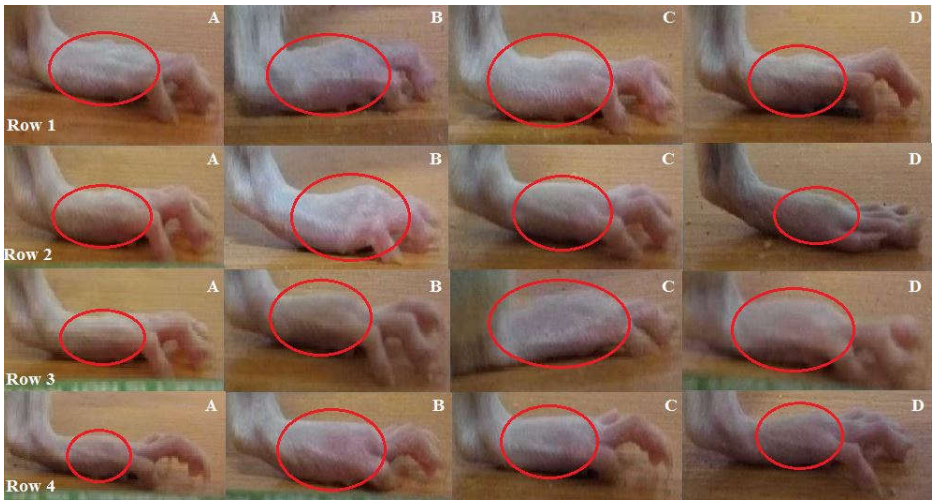


Figure 7. Rat paw of synthesized compounds. Row 1 represents [Ag-L^1], Row 2 shows (L^1), Row 3 is for control and Row 4 reveals standard diclofenac anti-inflammatory drug. From the above compounds [Ag-L^1] shows maximum reactivity by lowering level of inflammation in the paw more effectively than standard: [AgL^1] > (L^1) > diclofenac sodium > control.

Antioxidant

Different concentrations of Trolox (0.0005 g in 10 mL ethanol) 1.9, 15.6, 31.25, 125, 500 and 1000 mM, respectively were taken in glass bottles, in each bottle add 0.05 mL methanolic solution of DPPH. Absorbance of the reacting mixture was noted at 570 nm. IC_{50} values were calculated from 15 to 120 min. Test sample dilutions were also prepared from the following method. Trolox was used as reference antioxidant drug [43]. Data is given in (Table 3).

Table 3. Antioxidant activity.

Compound	Variation of IC_{50} with different time (min)				
	15 min	30 min	45 min	1 hour	2 hour
L^1	29.08	27.3	23.31	22.06	20.53
[Ag-L^1]	54.32	46.113	40.90	36.88	26.88
L^2	29.66	27.07	26.69	23.09	19.05
[Ag-L^2]	34.37	30. 08	29.36	28.30	27.44
L^3	32.83	29.75	26.33	24.68	22.59
[Ag-L^3]	40.90	37.05	35.63	32.09	30.80
Trolox	2.35	2.33	2.34	2.32	2.30

CONCLUSION

Three new Schiff bases and their Ag(I) complexes were synthesized and characterized by ^{1}H NMR spectra confirmed formation of ligands. FT-IR data confirmed the ligands are bidentate. Molar conductance values show non-electrolyte behavior of the complexes. IC_{50} values showed more activeness of metal complexes while Schiff base ligands showed no reactivity towards cytotoxicity. Synthesized metal complexes killed 3T3 primary mouse embryonic fibroblast fast

growing cells. Human cancerous cells were not easy to grow in ordinary research labs. Cancerous cells are also fast growing cells which showed uncontrolled growth, so we might predict that these synthesized drugs may also serve as anti-cancerous under special conditions. Antibacterial results showed that (L^1) and (L^2) were active against *Staphylococcus aureus* and all Ag(I) complexes were all active and killed bacterial species significantly while (L^3) is not active. Antioxidant screening shows that all the synthesized compounds showed activity towards lower concentration as we move from 15 min to 2 hour time interval while metal complexes showed more significant results than ligands. (L^1) and [Ag-L^1] behaves more significant anti-inflammatory drugs as compared to standard.

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