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Scientific paper

Synthesis, Characterization, Anti-Glycation, and Anti-Oxidant Activities of Sulfanilamide Schiff Base Metal Chelates

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Abstract

The current study reports synthesis, structure establishment, anti-glycation, and anti-oxidant activities of ligand 4-[(2-hydroxynaphthalene-1-ylmethylene)-amino]-benzenesulfonamide (L) and its coordination compounds with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) metal ions. The analytical techniques used (UV-Vis, FT-IR, CHN/S) confirmed the bidentate nature of the ligand, coordinating *via* O and N atoms in 2:1 ligand-to-metal ratio. The TG/DTA anylsis displayed that these compounds are thermally stable. Furthermore, the synthesized compounds were evaluated for their anti-glycation and antioxidant potential and showed significant activities with IC_{50} values range 184.11–386.34 μM and 37.05–126.27 μM, respectively. The Mn (IC_{50} = 184.11 ± 2.11 μM), Ni (IC_{50} = 211.26 ± 1.46 μM), Cu (IC_{50} = 254.56 ± 1.16 μM), and Zn (IC_{50} = 276.43 ± 2.14 μM) metal complexes exhibited substantial anti-glycation activity and comparatively better activity than the standard rutin (IC_{50} = 294.4 ± 1.50 μM), whereas Zn complex (IC_{50} = 37.05 ± 1.53 **μ**M) also showed better DPPH radical scavenging activity than the standard *tert*-butyl-4-hydroxyanisole (IC_{50} = 44.7 ± 1.21 μM).

Keywords: 4-[(2-Hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide (L), Coordination Compounds, Anti-oxidant activity, Anti-glycation activity

1. Introduction

Coordination chemistry deals with the study of coordination compounds or metal complexes. The group of ten elements (*i.e.* V, Cr, Fe, Mn, Co, Cu, Ni, Mo, Zn, and Cd) form many complexes with various biomolecules to execute different biological functions.[1,2] These metal complexes are required for our bodies in very small quantities, but their excess or deficiency can cause many serious diseases.[3,4] The clinical and commercial importance of metal complexes as medicinal drugs is increasing day by day for the treatment of various diseases.[5,6] The synthesis of metal complexes as chemotherapeutic agents in clinical application has shown significant progress in medicinal chemistry to fight against several human diseases, such as to treat different types of cancers, tumors, diabetes mellitus, anti-inflammation, possessing antifungal activity and acting against a wide range of bacterial diseases.[7–9] Recently, the metal complexes of transition elements have shown great importance in materials synthesis, catalysis and photochemistry.[10,11] The platinum metal complexes including cisplatin, carboplatin and nedaplatin are widely used drugs for cancer chemotherapy.[12] Copper(II), zinc(II), vanadium(V) and oxidovanadium(V) metal complexes have been reported for their excellent antibacterial urease enzyme inhibition and catalytic properties.[13–17]

According to the literature, sulfonamides have a variety of bioactivities, including antitumor, antimalarial, antimicrobial, antithyroid, antidiabetic, anti-HIV/AIDS, anti-parasitic, antiepileptic, and dihydropteroate synthetase inhibitors activities.[18–21] Sulfonamide metal chelates derivatives have also been reported for their anti-inflammatory, antidiabetic, anti-HIV, anticancer, anti-carbonic anhydrase, diuretic, hypoglycemic, antithyroid, antimalarial, antitumor, anti-angiogenic, anti-tubercular, antibacterial, and antifungal activities.[22–25] Moreover, gold sulfonamide chelates were also found to have applications for the treatment of skin disorders and rheumatoid arthritis.[26]

Schiff bases are widely studied compounds due to their structural resemblance with the natural bioactive molecules and ease of synthesis of diverse structures.[27,28] The importance of Schiff base complexes in supramolecular chemistry, catalysis and material science, separation and encapsulation processes, biomedical applications and formation of compounds with unusual properties and structures has been well recognized and reviewed.[29–31] Sulfonamides Schiff base complexes with cobalt(II), copper(II), nickel(II) and zinc(II) have shown significant *in vitro* antibacterial, antifungal, and cytotoxic properties. The *N,N*-chelating half-sandwich ruthenium(II) *para*-cymene complexes containing sulfonamide moieties also showed a broad range of therapeutic applications, which include the inhibition of various isoforms of carbonic anhydrases (CAs).[32]

Glycation is a reaction of blood sugar with the proteins like collagen; when this reaction occurs in a great extent advanced glycation products (AGEs) are formed which may further degrade protein and cause oxidative stress that damage cell membranes and produce diabetic complications such as neuropathy and diabetes retinopathy which further increase the rate of the aging processes.

Oxidative stress is the main aspect of all living systems which occurs due to the excess of free radicals. Due to oxidative stress, biochemical energy is converted into adenosine triphosphate with the help of oxygen, this biochemical reaction generates reactive oxygenated species (ROS). These ROS can damage lipids, proteins, and DNA by oxidation and cause many diseases such as cancer, brain disorders, rheumatoid arthritis, atherosclerosis, obesity, aging, diabetes and skin disease.[33] Antioxidant compounds are used as health-protecting factors in food playing an important role in preventing many diseases. The antioxidant compounds obtained from plants such as carotenes, phenolic acids, vitamin C and E, phytate, and phytoestrogens were found to be very helpful in decreasing the risks of many diseases. A number of synthetic compounds have also been reported having remarkable anti-oxidant properties.[34] The cosmetic and food industries are funded by several companies to promote the research of the synthesis of glycation-inhibiting ingredients and anti-oxidants in order to discover new anti-aging compounds for keeping skin youthful for a prolonged period. The latest research focuses on finding the ways for the inhibition of AGEs formation, and on reducing oxidative stress with the objective of promoting health by treating degenerative changes and mitigating the effect of lifestyle-related diseases.[35]

Earlier, we have reported anti-glycation and anti-oxidant properties of isatin containing hydrazide Schiff base metal complexes.[36] In the continuation of exploring metal complexes for bioactivities, herein we have synthesized 4-[(2-hydroxynaphthalen-1-ylmethylene)amino]benzenesulfonamide Schiff base ligand (L) and its metal (Mn, Co, Ni, Cu, Zn) complexes for the evaluation of anti-glycation and anti-oxidant activities.

2. Experimental

2. 1. Physical Parameters

Elemental (CHN/S), TG/DTA, and UV-Vis and metal content analyses were done on Perkin Elmer`s 2400 Series II and Diamond TG/DTA, Lambda 35 UV-Vis spectrophotometer, and Analyst 800 atomic absorption spectrophotometer, respectively. FT-IR were performed by Thermoscientific iS10 IR spectrophotometer in the region 4000–600cm^{-1}. Bruker 300 MHz spectrometer was used for ^{1}H NMR experiments. EI-MS were measured on Finnigan MAT-311A (Germany) mass spectrometer. Molar conductance was measured on Thermoscientific Orian 5 Star meter.

2. 2. Materials and Methods

Analytical grade chemicals (Sigma-Aldrich) sulfanilamide, 2-hydroxynaphthaldehyde, acetic acid, ammonium acetate and metal salts *viz* $MnSO_4{\cdot}H_2O$, $Co(CH_3COO)_2{\cdot}4H_2O$, $Ni(CH_3COO)_2{\cdot}4H_2O$, $CuCl_2{\cdot}2H_2O$, and $Zn(CH_3COO)_2{\cdot}2H_2O$ were used for synthesis. Bovine serum albumin (BSA) was obtained from Research Organics (Cleveland, USA).

2. 3. Synthesis of 4-[(2-Hydroxynaphthalen-1-ylmethylene)amino]benzenesulfonamide ligand (L)

0.5 mol of 2-hydroxynaphthaldehyde was added to 50 mL methanol with 2 to 3 drops of acetic acid and then added equimolar amount of sulfanilamide and refluxed for about 8 hours. The solvent was evaporated, precipitate obtained, dried and recrystallized from ethanol (Figure 1).

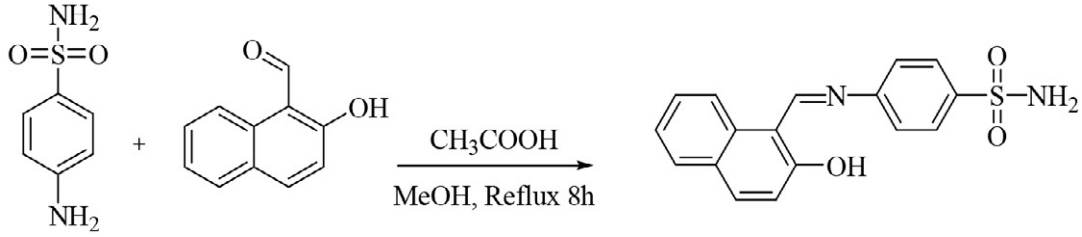


Figure 1. Synthesis of 4-[(2-hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide ligand (L)

Yield 80%, m.p. 278 °C. FT-IR ν_{max} 3290 (-OH, NH), 1622 (-C=N-), 1347 (O=S=O), 1586 (-C=C-) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ 6.87 (s, 1H, OH), 9.68 (s, 1H, CH=N), 8.52 (d, 2H, Ar, *J* = 8.7 Hz), 7.97 (d, 2H, Ar, *J* = 8.3 Hz, 6.88 (d, 1H, *J* = 7.4 Hz), 7.02 (d, 1H, *J* = 7.4 Hz), 7.58 (d, 2H, Ar, *J* = 7.6 Hz), 7.44 (m, 2H). EI-MS *m/z* 326 (M^+) 310, 246, 170, 157, 153, 77. Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.85; S, 9.82. Found: C, 62.51; H, 4.30; N, 8.79; S, 9.80.

2. 4. Synthesis of 4-[(2-Hydroxynaphthalene-1-ylmethylene)amino] benzenesulfonamide Ligand Metal Chelates

$MnSO_4{\cdot}H_2O$, $Co(CH_3COO)_2{\cdot}4H_2O$, $Ni(CH_3COO)_2{\cdot}4H_2O$, $CuCl_2{\cdot}2H_2O$, and $Zn(CH_3COO)_2{\cdot}2H_2O$ metal salts were refluxed with the ethanolic solution of 4-[(2-hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide ligand (L) and ammonium acetate for 6 h. Then, the solvent was evaporated and the obtained precipitates were isolated and washed with water. The structures of these compounds were confirmed by UV/Vis, FT-IR spectroscopy and CHN/S analysis, while thermal stability was measured by TG/DTA analysis.

$Mn(L)_2 \cdot 2H_2O$. Yield 83%, m.p. 235 °C. FT-IR ν_{max} 3480 (H_2O), 3278 (-OH, NH), 1615 (-C=N-), 1348 (O=S=O), 1587 (-C=C-) cm^{-1}. Anal. Calcd for $C_{34}H_{26}N_4O_6S_2Mn$: C, 55.06; H, 4.08; N, 7.55; S, 8.65. Found: C, 55.01; H, 4.01; N, 7.51; S, 8.60. Electrical conductance (DMF, μScm^{-1}): 5.22.

$Co(L)_2 \cdot 2H_2O$. Yield 84%, m.p. 170 °C. FT-IR ν_{max} 3480 (H_2O), 3278 (-OH, NH), 1615 (-C=N-), 1348 (O=S=O), 1587 (-C=C-) cm^{-1}. Anal. Calcd for $C_{34}H_{30}N_4O_8S_2Co$: C, 54.76; H, 4.06; N, 7.51; S, 8.60. Found: C, 54.73; H, 4.01; N, 7.47; S, 8.51. Electrical conductance (DMF, μScm^{-1}): 9.53.

$Ni(L)_2 \cdot 2H_2O$. Yield 87%, m.p. 250 °C. FT-IR ν_{max} 3480 (H_2O), 3278 (-OH, NH), 1615 (-C=N-), 1348 (O=S=O), 1587 (-C=C-) cm^{-1}. Anal. Calcd for $C_{34}H_{30}N_4O_8S_2Ni$: C, 54.78; H, 4.06; N, 7.52; S, 8.60. Found: C, 54.70; H, 4.02; N, 7.46; S, 8.64. Electrical conductance (DMF, μScm^{-1}): 0.25.

$Cu(L)_2 \cdot 2H_2O$. Yield 85%, m.p. 210 °C. FT-IR ν_{max} 3480 (H_2O), 3278 (-OH, NH), 1615 (-C=N-), 1348 (O=S=O), 1587 (-C=C-) cm^{-1}. Anal. Calcd for $C_{34}H_{30}N_4O_8S_2Cu$: C, 54.43; H, 4.03; N, 7.47; S, 8.55. Found: C, 54.40; H, 4.01; N, 7.41; S, 8.49. Electrical conductance (DMF, μScm^{-1}): 53.9.

$Zn(L)_2 \cdot 2H_2O$. Yield 81%, m.p. 250 °C. FT-IR ν_{max} 3480 (H_2O), 3278 (-OH, NH), 1615 (-C=N-), 1348 (O=S=O), 1587 (-C=C-) cm^{-1}. Anal. Calcd $C_{34}H_{30}N_4O_8S_2Zn$: C, 54.29; H, 4.02; N, 7.45; S, 8.53. Found: C, 54.25; H, 4.01; N, 7.38; S, 8.44. Electrical conductance (DMF, μScm^{-1}): 2.02.

2. 5. Anti-Oxidant (DPPH Radical Scavenging) Protocol

1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radical was used to measure the scavenging activity of ligand and metal complexes by using literature protocols. The reaction matrix consists of 5 μL test sample (1 mM in DMSO) and 300 μM DPPH (95 μL) and ethanol as the solvent. After 30 min of incubation at 37 °C, the absorbance of test samples was measured at 515 nm. All the samples were tested in triplicate. The following formula was used to calculate percent radical scavenging activity, whereas DMSO was used as a control.

$$\%\ \text{inhibition} = \frac{1 - \text{Absorbance of analyte}}{\text{Absorbance of the control group}} \cdot 100$$

50% of DPPH scavenge radicals represented by IC_{50} values. *tert*-Butyl-4-hydroxyanisole was used as the control. The anti-oxidant activities with IC_{50} values were measured according to the reported procedures.[37]

2. 6. Anti-Glycation Activity

Bovine Serum Albumin (10 mg/mL), anhydrous D-glucose (14 mM), and 0.1 M phosphate buffer (pH 7.4) containing sodium azide (30 mM) and various concentrations of the tested compounds in DMSO were incubated at 37 °C for 9 days. After 9 days, fluorescence (excitation, 330 nm; emission, 440 nm) was measured against blank. Rutin was taken as the standard anti-glycation agent. The AGE % inhibition was calculated by given formula:

$$\%\ \text{inhibition} = \frac{1 - \text{Fluorescence of analyte}}{\text{Fluorescence of the control}} \cdot 100$$

The anti-glycation activities with IC_{50} values were measured according to the reported procedures.[38]

3 Result and Discussion

3. 1. Chemistry

The literature revealed that metal complexes may be useful candidates in drug development process, therefore these compounds were synthesized and evaluated for their various physical parameters as well as bioactivities.

The ligand and its metal chelates were coloured, non-hygroscopic in nature, stable in air, have sharp melting points and were obtained with good yield. All metal chelates including the ligand were insoluble in hexane, chloroform, water, and ethanol although they were found to be soluble in dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF). The electrical conductance values for metal chelates in DMF solvent were found to be 0.25 to 53.9 $\mu S/cm^{-1}$. These values indicate the non-electrolytic

nature of metal chelates and the ligand are shown in Table S.1 (see Supp. data).

3. 2. Molecular Formula of the Ligand and Metal Complexes

The CHN/S elemental micro-analysis data agree well with the proposed formulae for 4-[(2-hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide ligand (L) and also confirm the composition of all synthesized metal chelates (Figure 2). The elemental analysis results show that calculated values are in close agreement with the values found. Elemental analysis confirmed the formula of the ligand and its metal complexes with 1:2 metal ligand ratio indicating the bidentate nature of the ligand as shown in Table S.2 (see Supp. data).

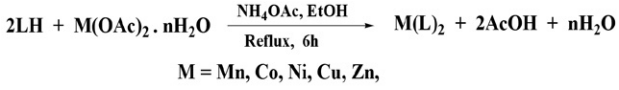


Figure 2. Proposed reaction for the synthesis of metal chelates

3. 3. Electronic Spectra

The UV-Vis spectra (see Supp. data Figures S.3–S.8) of 4-[(2-hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide (L) and its metal chelates were determined in DMSO solutions and show absorption bands at a longer wavelength with increasing intensity as shown in Table S.3 (see Supp. data). The ligand showed characteristic absorption bands at 315 and 364 nm. These bands were assigned to $\pi \rightarrow \pi^*$ intra ligand transitions. The UV-Vis spectra of all metal complexes showed bathochromic shifts [$Mn(L)_2$, 467 nm], [$Co(L)_2$, 471 nm], [$Ni(L)_2$, 473 nm], [$Cu(L)_2$, 470 nm], [$Zn(L)_2$, 472 nm] that were taken as an indication for metal complexation. These shifts might be attributed to the d-d-transitions. There were characteristic electronic transitions within the range of 260 nm to approximately 380 nm, that were also observed; these bands being unique for the electronic inter-ligand $\pi \rightarrow \pi^*$ transitions. Ligand to metal charge transfer (LMCT) peaks were also observed in a distinct region, *i.e.* within the range of 412 nm onwards, and these are a characteristic feature of nitrogen and oxygen atoms charge transfer to the central metal atoms.

3. 4. IR Spectroscopy

The data obtained from FT-IR spectra (see Supp. data Figures S.9–S.14) of some important functional groups of 4-[(2-hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide (L) and its metal chelates are presented in Table S.4 (see Supp. material). The IR spectrum of the ligand showed strong absorption bands at 1622 and 3290 cm^{-1}, which were attributed to the characteristic band of the ν(-C=N-) and ν(-OH) or -NH groups respectively. The sharp bands observed at 1347 cm^{-1} are due to -S=O stretching vibration. FT-IR spectral calculation revealed that for the ligand, which may act as a bidentate according to its structure, is expected that FT-IR measurements will be highly indicative with respect to the complexation behavior with various metal ions. Peaks in 3400 to 3500 cm^{-1} region support the observation of water molecules participating in the complex formation; this being further confirmed by CHN/S and thermogravimetric data. In the case of metal complexes, the peaks for azomethine group (-C=N-) were shifted from 1622 cm^{-1} to 1615, 1612, 1610, 1609, 1608 cm^{-1} and hydroxy group (–OH) peaks were shifted from 3290 cm^{-1} to 3278, 3260, 3248, 3240, 3237 cm^{-1} for $Mn(L)_2$, $Co(L)_2$, $Ni(L)_2$, $Cu(L)_2$ and $Zn(L)_2$ complexes, respectively. The changes in the frequency of the peaks indicated that these two groups are involved in coordination. Only spectra of metal complexes showed these new bands, which were thus established as those participating in these donor groups. The band at 1347 cm^{-1} for the $-SO_2$ group remains almost unaltered in the chelates, demonstrating that $-SO_2$ group is not contributing to the coordination.

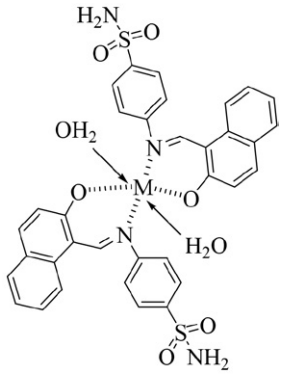
3. 5. Thermogravimetric Analysis of Ligand and Its Metal Chelates

The ligand 4-[(2-hydroxynaphthalene-1-ylmethylene)amino]benzenesulfonamide and its metal chelates were subjected for thermal stability profile. According to the TGA thtrmograms (see Supp. data Figures S.15–S.20) the ligand showed no weight loss upon heating till 250 °C. The further TGA process of the ligand was carried out which showed thermal decomposition in two stages. In the first stage the TGA curve of thermal decomposition was observed between 250–300 °C with weight loss of 1.85%, while the second stage was observed between 300–350 °C with weight loss of 39.5%. DTA thermogram showed one exothermic peak at 328 °C, while two endothermic peaks appeared at 69.42 °C and 270 °C, these may be due to some physical or chemical change phenomenon occurring during weight loss, such as melting, phase change, chemisorptions etc. The TGA of $Mn(L)_2$ complex showed thermal decomposition in three stages. In the first stage the TGA curve of thermal decomposition was observed between 150–200 °C with weight loss of 5.78%, this might be due to the dehydration process. The second and the third stages were observed between 200–250 °C (13.7%), and 250–350 °C (28.1%.) These stages correspond to the decomposition of organic part of metal complex. The DTA thermogram showed three endothermic peaks which were observed at 172 °C, 219 °C, and 326 °C. The TGA of $Co(L)_2$ complex showed thermal decomposition in two stages. In the first stage the TGA curve of thermal decomposition was observed between 150–200 °C with weight loss of 3.6%, the second stage was observed within the temperature range

200–350 °C with weight loss of 59.04%. These weight losses are linked with the loss of water molecules and disintegration of the ligand molecule. The two endothermic peaks were spotted at 115 °C and 225 °C in DTA. The TGA of $Ni(L)_2$ complex showed thermal decomposition in three stages, *i.e.* 150–250 °C, 250–350 °C and 350–410 °C with weight loss of 39.9%, 11.79%, and 16.05%, respectively. These weight losses are due to the dehydration breakdown of ligand. In the DTA thermogram three endothermic peaks appeared at 127 °C, 325 °C, and 388 °C. The TGA of $Cu(L)_2$ complex showed thermal decomposition in two stages. In the first stage the TGA curve of thermal decomposition was observed between 150–200 °C with weight loss of 4.14% (dehydration), while the second thermal putrefaction chelating molecule was observed at 200–350 °C with weight loss of 28.07%. Three endothermic peaks were marked in DTA thermogram at 91 °C, 246 °C, and 300 °C. The thermal disintegration of $Zn(L)_2$ complex was observed in three stages. In the first stage the thermal decomposition was observed at 150–270 °C with weight loss of 4.23%, possibly due to the dehydration; the second at 270–370 °C (28.7%), while the third stage was observed at 400–460 °C with weight loss of 10.89%. The DTA thermogram showed five endothermic peaks which were observed at 108 °C, 148 °C, 251 °C, 346 °C, and 441 °C. These values are closely related to the calculated values. The metal chelates total weight loss thermal stability was found to be as Cu > Zn > Mn > Co > Ni (Table S.5, see Supp. data).

3. 6. Structural Interpretation

The data of spectroscopic, elemental and thermal analyses revealed that metals are coordinated *via* N and O atoms of ligand molecules in 1:2 M/L ratio (Figure 3). It is reported in the literature that copper can form the octahedral coordinated metal complexes such as $[Cu(Hmbm)_2(OAc)_2]$, which was reported as an octrahedral complex. Hmbm is bonded to the Cu(II) ion in a chelating mode through its nitrogen and oxygen atoms, and two carboxylic oxygen atoms complete the octahedral coordination. The coordination of a water molecule was confirmed by FT-IR and XRD data.[40] For the same cause, the synthesized complexes have the octahedral geometry.



M = Mn, Co, Ni, Cu, Zn,

Figure 3. The proposed structures for metal chelates

4. Biological Screening

4. 1. Anti-Glycation Activity

4-[(2-Hydroxynaphthalene-1-ylmethylene)amino] benzenesulfonamide ligand (L) and its metal chelates were tested for their anti-glycation activity, using rutin (IC_{50} = 294.4 ± 1.50 **μ**M) as the standard (Table 1). They showed excellent anti-glycation activity. The ligand (IC_{50} = 265.11 ± 1.86 μM) and its metal chelates including $Mn(L)_2$ (IC_{50} = 184.11 ± 2.11 **μ**M), $Zn(L)_2$ (IC_{50} = 211.26 ± 2.14 **μ**M), $Ni(L)_2$ (IC_{50} = 254.56 ± 1.73 **μ**M), $Cu(L)_2$ (IC_{50} = 276.43 ± 1.16 **μ**M) showed outstanding anti-glycation activity, whereas, $Co(L)_2$ (IC_{50} = 386.34 ± 1.46 **μ**M) was observed as a weak anti-glycating agent. Among them, $Mn(L)_2$ complex showed the highest activity and it was found to be many fold more active than the standard rutin. However, $Zn(L)_2$, $Ni(L)_2$, and $Cu(L)_2$ are comparatively less active than $Mn(L)_2$ complex, although they were also found to have better activities than the standard. The activity pattern of these complexes can therefore be depicted as: $Mn(L)_2$ > $Zn(L)_2$ > $Ni(L)_2$ > $Cu(L)_2$ > $Co(L)_2$ (see Supp. data S.21–S.24). It was found that these chelates have capability to interact with proteins or glucose in a great extent and can obstruct the advancement of glycation. The active compounds may insert into hydrophobic cavities of BSA followed by the inhibition of advance glycation. $Mn(L)_2$ has elevated level of insertion into the slots of BSA protein.

Table 1. Anti-glycation Activity of Ligand and Respective Chelates

S#	Compounds	Anti-Glycation IC_{50} (μM ± SEM[a])
1.	Ligand	265.11 ± 1.86
2.	$Mn(L)_2{\cdot}2H_2O$	184.11 ± 2.11
3.	$Co(L)_2{\cdot}2H_2O$	386.34 ± 1.46
4.	$Ni(L)_2{\cdot}2H_2O$	254.56 ± 1.73
5.	$Cu(L)_2{\cdot}2H_2O$	276.43 ± 1.16
6.	$Zn(L)_2{\cdot}2H_2O$	211.26 ± 2.14
7.	Rutin	294.4 ± 1.50

[a] SEM is the standard error of the mean; [b] rutin is standard inhibitor for anti-glycation activity

4. 2. Antioxidant Assay

4-[(2-Hydroxynaphthalene-1-ylmethylene)amino] benzenesulfonamide ligand (L) and its metal chelates were assessed for DPPH radical scavenging activity (Table 2). Ligand (IC_{50} = 65.58 ± 1.29 **μ**M) itself was found to be weakly active, while its metal complex $Zn(L)_2$ (IC_{50} = 37.05 ± 1.53 **μ**M) showed excellent antioxidant activity as com-

pared to the standard *tert*-butyl-4-hydroxyanisole (IC_{50} = 44.7 ± 1.21 **μM**). The metal complexes such as $Mn(L)_2$ (IC_{50} = 76.1 ± 1.44 **μM**), $Cu(L)_2$ (IC_{50} = 86.11 ± 1.12 **μM**), $Co(L)_2$ (IC_{50} = 112.14 ± 1.11 **μM**), and $Ni(L)_2$ (IC_{50} = 126.27 ± 1.54 **μM**) were found to be less active than the standard. The order of anti-oxidant potential of these chelates is $Zn(L)_2 > Mn(L)_2 > Cu(L)_2 > Co(L)_2 > Ni(L)_2$.

Table 2. Antioxidant Activity of Ligand and Respective Chelates

S#	Compounds	DPPH Radical Scavenging Activity IC_{50} (μM ± SEM[a])
1.	Ligand	65.58 ± 1.29
2.	$Mn(L)_2{\cdot}2H_2O$	76.1 ± 1.44
3.	$Co(L)_2{\cdot}2H_2O$	112.14 ± 1.11
4.	$Ni(L)_2{\cdot}2H_2O$	126.27 ± 1.54
5.	$Cu(L)_2{\cdot}2H_2O$	86.11 ± 1.12
6.	$Zn(L)_2{\cdot}2H_2O$	37.05 ± 1.53
7.	*tert*-butyl-4-hydroxyanisole[b]	44.7 ± 1.21

[a] SEM is the standard error of the mean; [b] *tert*-butyl-4-hydroxyanisole is standard inhibitor for antioxidant activity

5. Conclusion

4-[(2-Hydroxynaphthalene-1-ylmethylene)amino] benzenesulfonamide ligand (L) and its $Mn(L)_2$, $Co(L)_2$, $Ni(L)_2$, $Cu(L)_2$, $Zn(L)_2$ chelates were investigated for anti-glycation and DPPH radical scavenging activity. Among these chelates $Mn(L)_2$ (IC_{50} = 184.11 ± 2.11 μM), $Zn(L)_2$ (IC_{50} = 211.26 ± 2.14 μM), $Ni(L)_2$ (IC_{50} = 254.56 ± 1.73 μM), and $Cu(L)_2$ (IC_{50} = 276.43 ± 1.16 μM) showed notable anti-glycation potential while $Zn(L)_2$ (IC_{50} = 37.05 ± 1.53 μM) showed excellent DPPH radical scavenging activity. The results show that these complexes have excellent potential towards anti-glycation activity. So, it is concluded that these complexes may serve as organometallic lead compounds in the drug development process to cure diabetic complications. However, further studies on the mechanisms of antioxidation and anti-glycation are required.

Acknowledgement

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Conflict of Interest

There is no conflict of interest

Supplementary Data

Tables S.1–S.5 and figures S.1–S.24 (proton NMR and mass spectrum of the ligand; UV-Vis, FT-IR and TGA/DTA spectra of the ligand and complexes; structure of complexes).

5. References

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Povzetek

Predstavljena raziskava opisuje sintezo, določitev strukture ter anti-glikacijske in antioksidativne lastnosti liganda 4-[(2-hidroksinaftalen-1-ilmetilen)amino]benzensulfonamida (L) ter njegovih koordinacijskih spojin z Mn(II), Co(II), Ni(II), Cu(II) ter Zn(II) kovinskimi ioni. Uporabljene analizne tehnike (UV-Vis, FT-IR, CHN/S) so potrdile bidentatno naravo liganda, ki se koordinira preko O in N atomov v razmerju liganda proti kovini 2:1. TG/DTA analiza je pokazala, da so te spojine termično stabilne. Za sintetizirane spojine smo določili tudi anti-glikacijske aktivnosti (IC_{50} vrednosti v območju 184.11–386.34 μM) ter antioksidativne lastnosti (IC_{50} vrednosti v območju 37.05–126.27 μM). Kovinski kompleksi Mn (IC_{50} = 184.11 ± 2.11 μM), Ni (IC_{50} = 211.26 ± 1.46 μM), Cu (IC_{50} = 254.56 ± 1.16 μM) in Zn (IC_{50} = 276.43 ± 2.14 μM) so izkazali precej boljše anti-glikacijske aktivnosti kot standard rutin (IC_{50} = 294.4 ± 1.50 μM). Kompleks s Zn (IC_{50} = 37.05 ± 1.53 **μ**M) pa je pokazal boljšo sposobnost lovljenja radikalov na DPPH testu kot standard *terc*-butil-4-hidroksianizol (IC_{50} = 44.7 ± 1.21 μM).