UJMR, Vol. 7 No. 2, December, 2022, pp. 87 - 91 E-ISSN: 2814 – 1822; P-ISSN: 2616 – 0668

https://doi.org/10.47430/ujmr.2272.013

Received: 17th November, 2022 Accepted: 2nd December, 2022

Antimicrobial activity of Bis-salicylaldehyde Ethylenediamine Schiff Base and Its Lanthanoids (III) Complexes

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Abstract

Schiff base readily form complex with metal ions and the resultant complexes especially from transition metals were extensively used in many fields of human endeavor including antimicrobial therapy. However, the potentials of Lanthanide-Schiff base complexes as an antimicrobial agent have not been adequately studied. This study aims to synthesize and determine the antimicrobial activity of Bis-salicylaldehyde ethylenediamine Schiff Base and its Lanthanoids (III) Complexes. The Dysprosium (III), Gadolinium (III), Neodymium (III) and Samarium (III) complexes of Schiff base derived from Salicylaldehyde and ethylenediamine were synthesized under reflux condition in ethanol and their antimicrobial activity were determined using disc diffusion method. Bis-salicylaldehyde ethylenediamine was a shiny crystalline yellow with a yield of 93% and its complexes were various sheds of yellow ranges from pale to dark, with percentage yield between 94-98%. The Bis-salicylaldehyde ethylenediamine had good activity against C. albican (32mm at 100mg/ml), A. niger (20mm at 100mg/ml) and Fusarium Spp (17mm at 100mg/ml) but its complexes had low (07-11mm at 100mg/ml) or no (06mm at 100mg/ml) activity against all the fungal isolates. The antibacterial activity of the Bis-salicylaldehyde ethylenediamine against E. coli (8mm at 100mg/ml), Pseudomonas (6mm at 100mg/ml) and Klebsiella (13mm at 100mg/ml) was lower than that of Ampiclox (between 17 to 20mm) and even though, all its Lanthanoid (III) complexes between 8 to 14mm at 100mg/ml) had higher antibacterial activity than the Bis-salicylaldehydeethylenediamine but still the activity of Lanthanoid (III) complexes was lower than that of Ampiclox. Considering the in-vitro antimicrobial activity exhibited by Bis-salicylaldehyde ethylenediamine and its Lanthanoid (III) complexes against bacterial and fungal isolates, both will not be potential antibacterial agent but Bis-salicylaldehyde ethylenediamine could be pontential antifungal agent. We therefore, recommend further researches geared toward exploring its full potentials for antifungal therapy.

Keywords: Bis-salicylaldehyde ethylenediamine, Schiff base, Lanthanoids, antibacterial, antifungal, activity

INTRODUCTION

Schiff bases are compound with a functional group that contains Carbon-Nitrogen double bond with Nitrogen connected to either an Aryl or Alkyl group (Gopu and Xavier, 2015). They are excellent coordinating ligands because of their high stability, good solubility in common solvents and flexibility in various chemical environment (Santhi and Radhakrishnan, 2013). Schiff base form complex with metal ions through coordinate bonds with many metal ions using azomethine and other groups (Shafaatian *et al*., 2015).

Application of Schiff base-Metal complex have been exploited widely with excellent result in corrosion prevention, lasers, lighting systems, fluoro-immunoassays, anticancer and antimicrobial agents among others (Naini *et al*., 2012; Usharani *et.al*., 2013; Mikhalyova *et al*., 2014; Pradhan and Kumar, 2015; Leandro *et al*., 2017). However, most of the successful applications of metal complexes of Schiff bases were in those formed using transition metals rather than lanthanoids. Although, luminescent properties of lanthanides were acknowledge and utility of Schiff base-Lanthanoid complexes were exploited in catalysis and photochemical industry but the potential of Schiff base complex with Lanthanoid as antimicrobial agents is yet to be harnessed (Santhi and Radhakrishnan, 2013; Lekha, 2014; Nworie, 2016). This is despite the several findings on the ability of Lanthanide metals to potentiates the killing activity of antibacterial agents through generation of free hydroxylic radicals and emergence of microorganism resistant to commonly used antimicrobial agents (Correa-ascencio *et al.*, 2010; Lekha, 2014). The challenge enforced by emerging resistant organisms, undoubtedly prompted the need to develop new generations of antimicrobial agents to treat disease caused by these organisms.

This study synthesized and determined the antimicrobial activity of Bis-salicylaldehyde ethylenediamine Schiff Base (Salen) and its Lanthanoid (III) Complexes of Dysprosium, Gadolinium, Neodymium and Samarium against some bacterial and fungal isolates in comparison to the standard antibiotics and antifungal agents respectively.

MATERIALS AND METHODS

Chemicals and solvents were purchased from Sigma Aldrich, London, and used as purchased without further purification. The glass wares were washed with detergent, rinsed with distilled water and soaked in (1:4) HNO_3 then rinsed again with distilled water and dried in an oven at 110ºC. The microbial isolates [Bacteria: *E. coli, Pseudomonas* and *Klebsiella Spp.* Fungi: *A. Niger, C. albican and Fusarium Spp.*] were obtained from the Department of Medical Microbiology, Federal Teaching Hospital (FTH), Katsina and identified at the Microbiology Department, Umaru Musa Yar'adua University (UMYU), Katsina. Nutrient and Potato Dextrose Agar were obtained from Mueller Hinton Agar, Himedia Laboratories Pvt. Ltd. Mumbai, India

Preparation of Bis-salicylaldehyde ethylenediamine (Salen)

Bis-salicylaldehydeethylenediamine is prepared through condensation of Ethylenediamine and Salicylaldehyde according to modification of Kendre *et al.*, (2014) in which 0.70ml of 10mmol of pure ethylenediaminewas dissolved in 25ml of boiling ethanol and then 2.10ml of 19.70mmol of salicylaldehyde was added. The reaction mixture was vigorously stirred with a magnetic stirrer on a hot plate for five (5) minutes at 80ºC and then left in an ice bath to form crystals. Crystals formed were filtered off and washed by a small amount of ice-cold ethanol and air dried.

Preparation of the Bis-salicylaldehyde ethylenediamine lanthanoid (III) metal complexes

Similar condensation method according to the modification of Kendre *et al.*, 2014 was employed in preparation of Bis-salicylaldehydeethylenediaminelanthaniod (III) metal complexes. A solution of 1mmol of respective Lanthanoid (III) nitrate in 40ml of ethanol was added drop wise to a boiled solution of 1mmol of Bis-salicylaldehyde ethylenediamine in 80ml of ethanol. The mixture was stirred at room temperature until precipitates developed which were then immediately removed, filtered, washed with ethanol and dried in a desiccator over anhydrous sodium sulphate for one week.

Determination of antimicrobial activity of Bis-salicylaldehyde ethylenediamine Schiff Base and its Lanthanoids (III) Complexes

In vitro antibacterial activity against isolates of *E. coli, Pseudomonas and Klebsiella Spp.* was determined by disc diffusion method (Sharma *et al.*, 2009). The suspension of each bacteria were smeared on to the solidified Nutrient Agar (N.A). Three concentrations [25, 50 and 100mg/ml] of Bis-salicylaldehydeethylenediamine Schiff base [in DMSO] and each of its Lanthanoid (III) complexes [in Benzaldehyde] were prepared through serial dilution and placed on the culture media before incubation at 37ºC for 24 hours. Activities were determined by measuring (in mm) the diameter of zone of inhibition, the results were compared with standard drug (Ampiclox). *In vitro* antifungal activity against isolates of *A. Niger, C. albican and Fusarium Spp.*, was determined in a similar manner with antibacterial activity using Potato Dextrose Agar (PDA) culture media, Ketoconazole standard and 48 hours incubation period.

RESULTS

Bis-salicylaldehydeethylenediamine Schiff base was a shiny crystalline yellow product with a good yield of 93% while its Lanthanoid (III) Complexes were different shades of yellow (Table 1).

Bis-salicylaldehyde ethylenediamine at 100mg/ml had highest activity against *Klebsiella spp* (13mm) and least activity against *Pseudomonas* (6mm) but its activity is inferior to Ampiclox against *Klebsiella Spp* (20mm) and *Pseudomonas* (17mm). Amongst the complexes, $[Gd_2(Salen)_3]$ at 100mg/ml had highest activity against *Pseudomonas* (13mm) and $[Sm_2(Salen)_3]$ at 100mg/ml had least activity against *E. coli* (6mm) (Table 2). Bis-salicylaldehyde ethylenediamine at 100mg/ml had highest activity against *C. albican* (32mm) and least activity against *Fusarium Spp* (17mm) and its activity is superior or comparable to Ketoconazole against *C. albican* (24mm) and *Fusarium Spp* (17mm) its Lanthanoid (III) complexes of Dysprosium and Samarium had at 100mg/ml no activity (06mm) against all the fungal isolates tested (Table 3).

Table 1: Physical Properties of the Bis-salicylaldehyde ethylenediamine (Salen) and its Lanthanoid (III) Complexes

Compound	Molecular Formula	Colour	Percentage Yield (%)
Salen	$C_{16}H_{16}N_2O_2$	Brightly shinny yellow	93
$[Dy_2(Salen)_3]$	$C_{20}H_{48}N_6O_6)_3Dy_2$	Pale yellow	96
$[Gd_2(Salen)_3]$	$C_{20}H_{48}N_6O_6)_3Gd_2$	Light yellow	97
$[Nd_2(Salen)_3]$	$C_{20}H_{48}N_6O_6)_3Nd_2$	Dark yellow	98
$[Sm_2(Salen)_3]$	$C_{20}H_{48}N_6O_6)_3Sm_2$	Light yellow	94

Salen = Bis-salicylaldehyde ethylenediamine

Table 2: Antibacterial profile of Bis-salicyldehyde ethylenediamine and its Lanthanoid (III) Complexes

	Zone of Inhibition								
Bacterial isolates	*E. coli*			*Pseudomonas*			*Klebsiella* spp.		
Concentration (mg/ml)	25	50	100	25	50	100	25	50	100
Salen	07	07	08	06	06	06	10	10	13
	08	08	09	07	08	09	07	08	08
$[Dy_2\ (Salen)_3]$									
$[Gd_2\ (Salen)_3]$	08	10	11	10	11	13	07	07	08
$[Nd_2\ (Salen)_3]$	07	07	09	07	09	09	09	11	14
$[Sm_2\ (Salen)_3]$	06	06	06	09	09	11	07	07	09
Ampiclox (20mcg)		18			17			20	

Salen = Bis-salicylaldehyde ethylenediamine
Key: 6mm (Disc diameter) -Indicate no activity

Table 3: Antifungal profile of Bis-salicylaldehyde ethylenediamine and its Lanthanoid (III) Complexes

	Zone of Inhibition								
Fungal isolates	*A. niger*			*C.albican*			*Fusarium* spp.		
Concentration (mg/ml)	25	50	100	25	50	100	25	50	100
Salen	06	07	20	15	19	32	06	10	17
$[Dy_2\ (Salen)_3]$	06	06	06	06	06	06	06	06	06
$[Gd_2\ (Salen)_3]$	06	06	09	06	06	06	06	06	06
$[Nd_2\ (Salen)_3]$	06	07	11	06	07	07	06	06	06
$[Sm_2\ (Salen)_3]$	06	06	06	06	06	06	06	06	06
Ketoconazole (10mcg)		24			25			19	

Salen = Bis-salicylaldehyde ethylenediamine, Disc diameter = 6mm and indicates no activity

DISCUSSION

Owing to the diameter of zone of inhibition, the Ligand has no activity (06mm) against *Pseudomonas* and very low (07mm) and moderate activity (13mm) against *E. coli* and *Klebsiella* respectively (Sani and Kurawa, 2016). Despite the slight potentiation of activity recorded through increasing concentration of the ligand and complex formation with Lanthanoids (Dysprosium, Gadolinium, Neodymium and Samarium), still the activity against the sensitive organism remained inferior to the standard used (Ampiclox). This finding is in line with observations made on antibacterial activity of new metal complex of La(III) ion with tetradentate Schiff base derived from Salicylaldehyde and Ethylenediamine (Kendre *et al.*, 2014). Also, the higher activity exhibited by Lanthanoid (III) complexes over the Ligand and increasing concentration of the compounds were earlier demonstrated with other Schiff base complexes especially using transition metals (Singh and Dhakarey, 2009; Prafullkumar *et al.*, 2012; Rehman *et al.*, 2013). This phenomenon of enhanced antibacterial activity of complex in comparison with the Ligand could be due to reported generation of free hydroxyl radicals of the Lanthanides and chelation capacity of the complex (Correa-ascencio *et al.*, 2010; Kendre *et al.*, 2014). However, inspite this antibacterial activity of the Ligand and potentiating effect of the activity by Ligand-Lanthanoids complex and increasing concentration of the compounds, both the Ligand and its Lanthanoids (III) complex cannot be good candidates for therapy against either Gram positive or Negative bacteria.

Interestingly, the antifungal activities shown by the ligand against the three fungal isolates [15mm, 19mm and 32mm at 25mg/ml, 50mg/ml and 100mg/ml] for *C.albican*, [06mm, 07mm and 20mm at 25mg/ml, 50mg/ml and 100mg/ml] for *A. Niger* and [06mm,10mm and 17mm at 25mg/ml, 50mg/ml and 100mg/ml] for *Fusarium spp* were at far or above those recorded for the standard used (Ketoconazole) 10mcg. However, its complexes with Dysprosium and Samarium are totally resisted (06mm) by all the three fungal isolates *at* all concentrations while others (Gadolinium and Neodymium) were either resisted (06mm) or shows low (07mm) to moderate (09-11mm) activity at highest concentrations. These findings are not in conformity with the Overtone's concept (Anjaneyulu *et al.*, 1986) and the Tweedy's chelation theory. According to Overtone's concept of cell permeability, the lipid membrane that surround the cell favour the passage of only lipid-soluble materials making lipophilicity an important factor in antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a greater extent due to overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of pi-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and thus blocking the various metabolic activities of microorganisms. The poor antifungal activity of the Lanthanoids (III) complexes notwithstanding, the Ligand (Bis-salicylaldehyde ethylenediamine) should be interrogated further on the ladder of antifungal agents.

CONCLUSION

Bis-salicylaldehyde ethylenediamine can be synthesized easily with good yield and harbor potentials for antifungal therapy above its Lanthanoids (III) complex of Dysprosium, Gadolinium, Neodymium and Samarium. Hence, further researches in this line are highly recommended to compliment the arsenal for control of fungal infections in the phase of emerging antimicrobial resistance.

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