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Synthesis and Screening of Biologically active Schiff bases of Benzothiazoles and its Zinc and Lanthanum metal complexes

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ABSTRACT

The substituted 2-Aminobenzothiazole and ethyl 2-(4-formyl-3-hydroxyphenyl)-4-methylthiazole-5-carboxylate in methanol mix together and heat the reaction mixture for overnight, It gives Schiff's bases (derivatives of substituted aminobenzothiazole) **3**.This compound **3** when treated with zinc chloride it gives zinc metal complex of Schiff's bases **4** and if compound **3** was treated with Lanthanum chloride gives Lanthanum metal complex of Schiff's bases **5**, which shows marked biological activities.

Keywords: 2-Aminobenzothiazole, Zinc chloride, Lanthanum chloride, Metal complex.

INTRODUCTION

The benzothiazole derivatives show wide range of biological activities which include analgesic[1], anti-inflammatory[2], antiviral[3], antibacterial[4] and anticancer activities.

Preparation and screening of 2-Aminobenzothiazole derivatives in vitro as potential antimicrobial activity, which shows remarkable antifungal activity[5]. Hugo Schiff reported the condensation of primary amines with carbonyl compounds known as Schiff's bases which reported in 1864[6]. Nowadays, Schiff base coordination chemistry has expanded enormously in the field of research. Advantages of Schiff base complexes for biological applications, bioinorganic chemistry, material science, supramolecular chemistry, catalysis and separation and summarize processes, and formation of compounds with unusual properties and structures has been well recognized and reviewed.[7]

Schiff Bases are characterized by the Imine (-N=CH-) group which carries out the mechanism of transamination and racemization reaction in biological system[8,9]

Several Schiff's bases are listed to get outstanding antibacterial, antifungal and anticancer activities[10,11,12,13].

Lanthanide complexes showed importance in cancer diagnosis and therapy. Lanthanide-based tiny molecules as well as nonmaterial's have been scrutinize as cytotoxic agents and constraint, in photodynamic treatment, radiation therapy, drug delivery.[14]

The Zn (II) complex has a very interesting and varied pharmacological activity. Zn (II) complex are effective against gastric mucosal injuries[15,16,17] shows a potent anti-ulcer activity and is also effective against Helicobacter pylori, a causative agent for stomach ulcers.

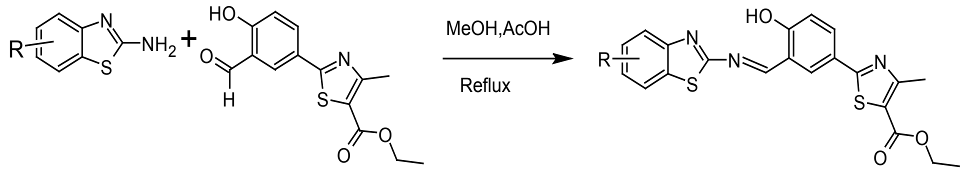
Present work

Experimental Procedure for Schiff's bases

The equimolar solutions of 2-aminobenzothiazole and ethyl 2-(4-formyl-3-hydroxyphenyl)-4-methylthiazole-5-carboxylate were stirred in 10 mL of methanol. The reaction mixture was then heated overnight for 12 to 14 hours. The completion of reaction was monitored by thin layer chromatography (TLC) using hexane: Ethyl Acetate (8:2). The reaction mixture was gradually cool at room temperature. The reaction mixture was then filtered and washed with 5 mL of methanol. The wet sample was dried at 50^{0}C in oven for 5 hours. The product obtained was yellow dry solid with the yield of 95%.

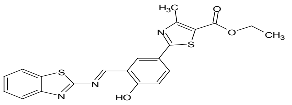
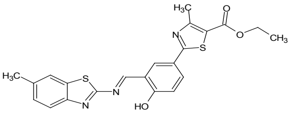
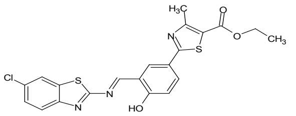
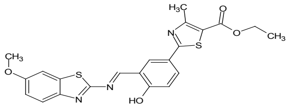
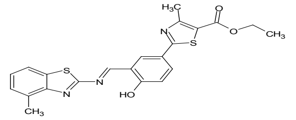
EXPERIMENTAL

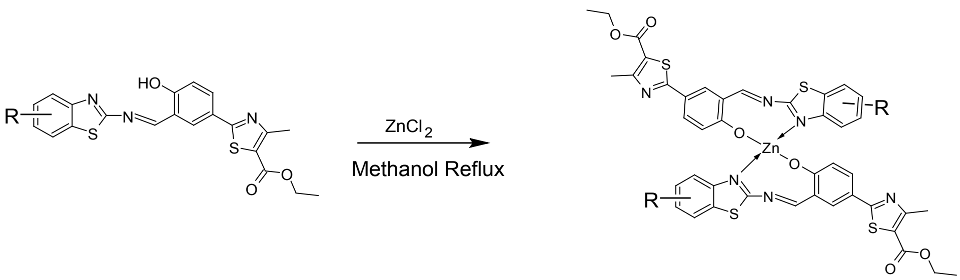
Infrared spectra were recorded in KBr disc on Shimadzu FTIR Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz spectrophotometer DMSO-d_6 as a solvent and TMS as an internal standard (chemical shift in δ values). Mass spectra were analyzed in Finnigan mass spectrometer. Purity of the compounds was checked by TLC on silica gel plates.



Scheme. 1

Table 1: Spectral Data of synthesized Schiff's Bases

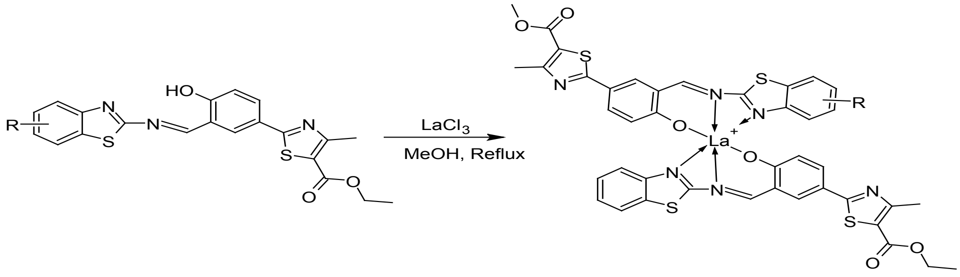
Sr. No	Structure	Mass	IR			^{1}HNMR				UV
			-O-H	O=C-OEt	C=N	Ar-OH	HC=N	O-CH_2-CH_3	O-CH_2-CH_3	
3a		423.9	2977	1710	1601	12.57	9.33	4.35	2.76	527
3b		438	2974	1709	1601	12.58	9.29	4.35	2.76	524
3c		457.9	2962	1713	1600	12.46	9.32	4.35	2.76	531
3d		454	2971	1707	1599	12.57	9.25	4.34	2.76	523
3e		438	2974	1709	1602	12.62	9.36	4.35	2.75	524



Scheme. 2

Experimental procedure for zinc metal complexes Synthesis of Bis[ethyl2-(4-hydroxy-3-{(E)-[(1,3-benzothiazol-2-yl)inimo]methyl} phenyl)-4-methyl-1,3-thiazole-5-carboxy- late]zinc(II)

The solution of ligand 3a-3e (2.36 mmol) was stirred in 30 mL methanol. Zinc chloride[18] solution (1.18 mmol in 10 mL methanol) was added dropwise in reaction mixture. The pH of 5.6 was adjusted by using sodium carbonate. The reaction mixture was then heated at 65-70^{0}C for overnight. The reaction mixture was allowed to cool at room temperature. The volume of reaction was reduced to 10 mL under vacuum. Then 5 mL of water was added by using dropping funnel in reaction mixture. It was stirred for 30 min and then filtered under vacuum. The wet solid obtained was recrystallized in water and methanol (7:3) at 60-65^{0}C. The orange crystalline product obtained (4a) was then dried at 75-80^{0}C for 12 hours.



Scheme. 3

Table 2: Biological Activities of Synthesized Schiff's Bases (Ligands)

Sr.No.	Microorganism	MIC value for Schiff's bases of benzothiazole in µg/mL 3a	3b	3c	3d	3e	Ciprofloxacin	Fluconazole
1	*C. albicans*	25	12.5	12.5	12.5	25	-	10
2	*E.coli*	12.5	12.5	12.5	12.5	25	2	-
3	Staphylococcus aureus	12.5	12.5	12.5	6.25	25	2	-
4	*Klebsiella pneumoniae*	12.5	12.5	12.5	12.5	25	1	-
5	*Bacillus subtilis*	12.5	12.5	12.5	6.25	25	2	-
6	Staphylococcus aureus	12.5	12.5	12.5	12.5	25	2	-

Table 3: Biological Activities of Synthesized Zinc Metal Complexes:

Sr.No.	Microorganism	MIC value for Zinc m/c in µg/mL 4a	4b	4c	4d	4e	Ciprofloxacin	Fluconazole
1	*C. albicans*	12.5	12.5	6.25	25	6.25	-	10
2	*E.coli*	25	12.5	12.5	25	12.5	2	-
3	Staphylococcus aureus	25	25	6.25	25	12.5	2	-
4	*Klebsiella pneumoniae*	25	12.5	12.5	25	12.5	1	-
5	*Bacillus subtilis*	25	25	6.25	25	12.5	2	-
6	Staphylococcus aureus	25	25	25	25	12.5	2	-

Table 4: Biological Activities of Synthesized Lanthanum Metal Complexes

Sr.No.	Microorganism	MIC value for Lanthanum M/C in µg/mL					Ciprofloxacin	Fluconazole
		5a	5b	5c	5d	5e		
1	*C. albicans*	12.5	6.25	6.25	6.25	12.5	-	10
2	*E.coli*	12.5	6.25	6.25	6.25	6.25	2	-
3	Staphylococcus aureus	6.25	6.25	6.25	6.25	6.25	2	-
4	*Klebsiella pneumoniae*	12.5	6.25	6.25	6.25	6.25	1	-
5	*Bacillus subtilis*	6.25	12.5	6.25	6.25	6.25	2	-
6	Staphylococcus aureus	6.25	12.5	6.25	6.25	6.25	2	-

Experimental procedure for lanthanum metal complexes

Synthesis of Bis[ethyl2-(4-hydroxy-3-{(E)-[(1,3-benzothiazol-2-yl)inimo]methyl} phenyl)-4-methyl-1,3-thiazole-5-carbo -xylate]lanthanum(II) chloride

The equimolar amount of ligand 3a to 3e & Lanthanum chloride (1.18mmol in 10 mL of methanol) were mixed in 30 ml methanol. It was added drop wise in reaction mixture and pH 5.6 was maintained by using sodium carbonate. Then heat mixture was to 65-70^{0}C for overnight 10 to 12 hours. The reaction mixtures gradually cool to ambient temperature. The volume of reaction was reduced to 10 mL under vacuum. Then 5 mL water was added drop wise to the reaction mixture with stirring for 30 minute. The reaction mixture filtered under vacuum. The wet solid was recrystallized using water and Methanol (7:3) at 60-65^{0}C and the orange crystalline product (5a) was dried for 12 hours.

Biological activity

Antibacterial assay

Antimicrobial of ligands and its metal complexes screened against three gram positive Staphylococcus aureus 1, *Staphylococcus aureus* 2 and *Bacillus subtilis*. Two *Gram-negative* like *Klebsiella pneumonia* and *Escherichia coli* and fungi *Candida albicans* to asset their potency as antimicrobial agent by minimum inhibition concentration (MIC) using microbiological method[19]. The test inoculums *Staphylococcus aureus* 1 ATCC 6538, *Staphylococcus aureus* 2 ATCC 33591, *Bacillus subtilis* ATCC 6051, *Klebsiella pneumonia* ATCC 4352, *E coli* ATCC 8739 and *Candida albicans* ATCC 24433. All ligands and its metal complexes have to be done with brain heart infusion (BHI) for Minimum inhibition concentration (MIC). Ingredients in brain heart Infusion 500 g/Liter contain Calf brain infusion form 200 g, beef heart infusion form 200 g, protease peptone 10 g dextrose 2 g sodium chloride 5 g disodium phosphate 2.5 g. Fluconazole and ciprofloxacin are used as standard. Micro broth dilution method was used for standard drugs. For facultative anaerobes, tubes were incubated at 37^{0}C for 48-72 h in carbon dioxide jar.

***In vitro* Antimicrobial Study**

The study of MIC values of Ligand and its metal complexes indicated that complexes are exhibit the highest antimicrobial activity than the ligand, these results are shown in table number 2, 3 and 4. ***C. albicans***, **(5a)** lanthanum Complex good Antimicrobial activity (12.5 µg/mL) up to MIC value and **(4a)** zinc complex (12.5 µg/mL) compared to **(3a)** Ligand (25 µg/mL). **(5b)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3b)** Ligand (12.5 µg/mL) as well as **(4b)** zinc complex (12.5 µg/mL). **(5c)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) and **(4c)** zinc complex (6.25 µg/mL) up to MIC value compared to **(3c)** Ligand (12.5 µg/mL). **(5d)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) and to **(3d)** Ligand (12.5 µg/mL) up to MIC value compared to **(4d)** zinc complex (25 µg/mL). **(4e)** zinc complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(5e)** lanthanum Complex (12.5 µg/mL) and **(3e)** Ligand (25 µg/mL).

E coli, **(5a)** lanthanum Complex and **(4a)** zinc complex moderate Antimicrobial activity (12.5 µg/mL) up to MIC value compared to **(3a)** Ligand (25 µg/mL). **(5b)** lanthanum complex good antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3b)** Ligand (12.5 µg/mL) and **(4b)** zinc complex (12.5 µg/mL). **(5c)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4c)** zinc complex (12.5 µg/mL) and **(3c)** Ligand (12.5 µg/mL). **(5d)** lanthanum complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3d)** Ligand (12.5 µg/mL) and **(4d)** zinc complex (25 µg/mL). **(5e)** lanthanum complex good antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4e)** zinc complex (12.5 µg/mL) and **(3e)** Ligand (25 µg/mL).

Staphylococcus aureus **1, (5a)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3a)** Ligand (12.5 µg/mL) as well as **(4a)** zinc complex (25 µg/mL). **(5b)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3b)** Ligand (12.5 µg/mL) as well as **(4b)** zinc complex (12.5 µg/mL). **(5c)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3c)** Ligand (12.5 µg/mL) as well as **(4c)** zinc complex (6.25 µg/mL). **(5d)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) and to **(3d)** Ligand (6.25 µg/mL) up to MIC value compared to **(4d)** zinc complex (25 µg/mL). **(5e)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4e)** zinc complex (12.5 µg/mL) as well as **(3e)** Ligand (25 µg/mL).

Klebsiella**, (5a)** lanthanum Complex and **(4a)** zinc complex moderate antimicrobial activity (12.5 µg/mL) up to MIC value compared to **(3a)** Ligand (25 µg/mL). **(5b)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3b)** Ligand (12.5 µg/mL) and **(4b)** zinc complex (12.5 µg/mL). **(5c)** lanthanum Complex good antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4c)** zinc complex (12.5 µg/mL) and **(3c)** Ligand (12.5 µg/mL). **(5d)** lanthanum complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to (3d) Ligand (12.5 µg/mL) and **(4d)** zinc complex (25 µg/mL). **(5e)** lanthanum complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4e)** zinc complex (12.5 µg/mL) and **(3e)** Ligand (25 µg/mL).

Bacillus subtilis **(5a)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3a)** Ligand (12.5 µg/mL) and **(4a)** zinc complex (25 µg/mL). **(5b)** lanthanum Complex and **(3b)** Ligand moderate Antimicrobial activity (12.5 µg/mL) up to MIC value compared to **(4b)** zinc complex (25 µg/mL). **(5c)** lanthanum Complex and **(4c)** zinc complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3c)** Ligand (12.5 µg/mL). **(5d)** lanthanum Complex and **(3d)** Ligand good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4d)** zinc complex (25 µg/mL). **(5e)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4e)** zinc complex (12.5 µg/mL) and **(3e)** Ligand (25 µg/mL).

***Staphylococcus aureus* 2, (5a)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3a)** Ligand (12.5 µg/mL) and **(4a)** zinc complex (25 µg/mL). **(5b)** lanthanum Complex and **(3b)** Ligand moderate Antimicrobial activity (12.5 µg/mL) up to MIC value compared to **(4b)** zinc complex (25 µg/mL). **(5c)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3c)** Ligand (12.5 µg/mL) and **(4c)** zinc complex (25 µg/mL). **(5d)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(3d)** Ligand (12.5 µg/mL) and **(4d)** zinc complex (25 µg/mL). **(5e)** lanthanum Complex good Antimicrobial activity (6.25 µg/mL) up to MIC value compared to **(4e)** zinc complex (12.5 µg/mL) and **(3e)** Ligand (25 µg/mL).

RESULTS AND DISCUSSION

Schiff bases are amorphous powder and metal complexes having crystalline powder. All the metal complexes are insoluble in water but soluble in DMSO. Metal complexes are stable at room temperature. On heating, they decompose at higher temperature. Analytical data of ligand and metal complexes are summarized below.

1.1 **In Ultraviolet-visible spectroscopy** observed that Schiff bases and metal complex shows different wavelength of maximum absorption. (3a) observed **527 nm** and its zinc complex.

1.2 (4a) observed **384 nm** and also lanthanum complex (5a) observed **363 nm**. Similarly (3b) observed **524 nm** and its zinc complex (4b) observed **384 nm** also lanthanum complex (5b) observed **363 nm**. (3c) observed **531 nm** and its zinc complex (4c) observed **386 nm** and also lanthanum complex (5c) observed **392 nm**. (3d) observed **523 nm** and its zinc complex (4d) observed **388 nm** also lanthanum complex (5d) observed **383 nm**. (3e) observed **527 nm** and its zinc complex (4e) observed **384 nm** and also lanthanum complex (5e) observed **363 nm**.

1.3 **In Infrared spectroscopy** IR spectra gives the valuable information about the functional group. Comparable studies of IR spectra of free ligand were compared with IR spectra of the complex. In IR spectra observed that slightly shifted hydroxyl value but in ester functional group and alkenes value are not changed in Schiff bases and its metal complexes. Hydroxyl value of Schiff bases and its metal complexes are as follows, in 3a to 4a and 5a are observed that **2977 cm^{-1}** to **2974 cm^{-1}** and **2981 cm^{-1}** respectively.

1.4 Similarly 3b to 4b and 5b are observed that **2974 cm^{-1}**, **2920 cm^{-1}** to **2979 cm^{-1}**, **2932 cm^{-1}** and **2974 cm^{-1}** respectively. In 3c to 4c and 5c are observed that **2962 cm^{-1}**, **2923 cm^{-1}** to **2973 cm^{-1}** and **2971 cm^{-1}** respectively. In 3d to 4d and 5d are observed that **2971 cm^{-1}**, **2924 cm^{-1}** to **2986 cm^{-1}** and **2981 cm^{-1}**, **3353 cm^{-1}** respectively. In 3e to 4e and 5e are observed that **2974 cm^{-1}**, **2921 cm^{-1}** to **3338 cm^{-1}**, **2975 cm^{-1}**, **2944 cm^{-1}** and **3353 cm^{-1}**, **2974 cm^{-1}**, respectively.

1.5 **^{1}H NMR Spectra** of the ligand taken in DMSO-d_6 solvent, azomethine proton in **3a** to **3e** observed in range between 9.25 to 9.36 ppm singlets, phenolic –OH singlet in range between 12.46 to 12.57 ppm and ethoxy group observed in range between 4.34 to 4.35 ppm (2H) quartet and 2.75 to 2.76(3H) triplet. Aromatic proton in range between 7.06 to 8.35 ppm.

1.6 **Mass Spectroscopy** Formation of Schiff bases is confirmed by presence of intense molecular ion peak.

CONCLUSION

All are novel Schiff bases have been synthesized and characterized by using different 2-amino benzothiazole derivatives and salicylic aldehyde derivative [Ethyl-2-(3-formyl-4-hydroxyphenyl)-4-methyl-1, 3-thiazole-5-carboxylate]. Novel transition metal complexes have been synthesized and characterized by spectroscopic techniques from above novel Schiff bases and zinc and lanthanum metal.

The spectral data shows that the stoichiometric ratio of the metal and ligand is 1:2. In zinc metal complexes, the ligand is bidentate which is coordinates through azomethine nitrogen of Schiff base and oxygen from salicylic fragment to the zinc metal. Similarly in lanthanum complexes, the ligand is tridentate which is coordinates through azomethine nitrogen of Schiff base, oxygen from salicylic aldehyde fragment and nitrogen from benzothiazole ring.

In vitro data shows the all lanthanum complexes shows the therapeutic benefit, particularly treatment for antifungal agents *C. albicans*, *E.coli*, *Klebsiella*, Staph 1 staph 2.

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Conflict of Interests

All authors are declaring that there is no conflict of interest regarding this publication.

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