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

D. G. ANUSE*, V. J. DESALE1, B. R. THORAT1, D. D. ANUSE2, S. G. JAGADHANI2, K. GEORGE ABRAHAM3 and R. S.YAMAGAR**

1Department of Chemistry, Government of Maharashtra’s Ismail Yusuf College of Arts Science and Commerce, Mumbai 400060, India.
2Veer Wajekar A. S. C. College, Phunde, Tal. Uran, Dist. Raigad, India.
3SIES College of Arts, Science and Commerce, Sion (West), Mumbai 400022, India.
4Chikitsak Samuha’s Patkar-Varde College of Arts, Science and Commerce, Goregaon (west), Mumbai 400 062, India.
*Corresponding author E-mail: devidasanuse@gmail.com

http://dx.doi.org/10.13005/ojc/370126

(Received: December 23, 2020; Accepted: February 18, 2021)

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 analgesic1, anti-inflammatory2, antiviral3, antibacterial4 and anticancer activities.

Preparation and screening of 2-Aminobenzothiazole derivatives in vitro as potential antimicrobial activity, which shows remarkable antifungal activity5. Hugo Schiff reported the condensation of primary amines with carbonyl compounds known as Schiff’s bases which reported in 18646. 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\textsuperscript{8,9}.

Several Schiff’s bases are listed to get outstanding antibacterial, antifungal and anticancer activities\textsuperscript{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\textsuperscript{14}.

The Zn (II) complex has a very interesting and varied pharmacological activity. Zn (II) complex are effective against gastric mucosal injuries\textsuperscript{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°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. \textsuperscript{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz spectrophotometer DMSO-d\textsubscript{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](image)

**Table 1: Spectral Data of synthesized Schiff’s Bases**

| Sr. No | IR | ¹H NMR |
|--------|----|--------|
|        | Structure | Mass | -O-H | O=C-OEt | C=N | Ar-OH | HC=N | O-CH\textsubscript{3}-CH\textsubscript{3} | O-CH\textsubscript{2}-CH\textsubscript{2} | UV |
| 3a     | ![Image](image) | 423.9 | 2977 | 1710 | 1601 | 12.57 | 9.33 | 4.35 | 2.76 | 527 |
| 3b     | ![Image](image) | 438 | 2974 | 1709 | 1601 | 12.58 | 9.29 | 4.35 | 2.76 | 524 |
| 3c     | ![Image](image) | 457.9 | 2962 | 1713 | 1600 | 12.46 | 9.32 | 4.35 | 2.76 | 531 |
| 3d     | ![Image](image) | 454 | 2971 | 1707 | 1599 | 12.57 | 9.25 | 4.34 | 2.76 | 523 |
| 3e     | ![Image](image) | 438 | 2974 | 1709 | 1602 | 12.62 | 9.36 | 4.35 | 2.75 | 524 |
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 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°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°C. The orange crystalline product obtained (4a) was then dried at 75-80°C for 12 hours.

| Sr.No. | Microorganism          | MIC value for Schiff’s bases of benzothiazole in µg/mL | 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  | -  |

| Sr.No. | Microorganism          | MIC value for Zinc m/c in µg/mL | 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            | 25          | 12.5         | 25     | 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          | 12.5         | 25     | 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            | 12.5          | -           |
| 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)iminomethyl]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°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°C and the orange crystalline product (5a) was dried for 12 hours.

Biological activity

Antimicrobial 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.[16] 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°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). (5d) 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).

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.

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.

1.4 $^1$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.

1.5 Mass Spectroscopy Formulation 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-thiaazole-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.

ACKNOWLEDGEMENT

We would like to thanks Post graduate and research centre, department of chemistry, Ismail Yusuf college Jogeshwari (E) 400060 India campus for providing the facilities to carry out the research work. We also express thanks the Management of Chikitsak Samuha’s Patkar-Varde College of Arts, Science and Commerce, Goregaon (W), Mumbai 400 062, India for consistent support and encouragement. We also appreciate the support provided by Veer Wajekar A. S. C. College, Phunde, and Tal. Uran, Dist. Raigad, and SIES College of Arts, Science and Commerce, Sion (W), Mumbai 400022.

Conflict of Interests

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

REFERENCES

1. B. H. M. Mruthyunjayaswami, B. K. Shanthaveerapa, Indian J. Chem 39B., 2000, 433-439.
2. D.J. Hadjipavlou-Litina, A. A. Geronikari, Drug design and discovery., 1998, 15(3), 199.
3. F. Gualliere, G. Brody, A. H. Fieldsteel, W. A. Skinner, J. Med. Chem., 1971, 14(6), 546.
4. I. Argyropoulou, A. Geronikaki, V. Paola, F. Zani, Arkivok VI., 2009, 89-102.
5. A. Catalano, A. Carocci, I Defrenza, M. Muraglia, A. carrier, F. Van Bambeke, A. Rosato, F. Carbo, C. Franchini, Eur. J. Med. Chem., 2013, 64, 357.
6. Z. Cimerman, S. Miljanic and N. Galic, *Croatica Chemica Acta.*, **2000**, 73(1), 81-95.
7. P. Singh, R. L. Goel and B. P. Singh, *J. Indian Chem. Soc.*, **1975**, 52, 958.
8. K. Y. Lau, A. Mayr, K. K. Cheung, *Inorg. Chem. Acta.*, **1999**, 285, 223.
9. A. S. Shawali, N. M. S. Harb, K. O. Badahdah, *J. Heterocycl Chem.*, **1985**, 22, 1397.
10. C. T. Supuran, M. Barboiu, C. Luca, E. Pop, M. E. Brewster, A. Dinculescu, *Eur. J. Med. Chem.*, **1996**, 31, 597.
11. G. Matela, *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, **2020**, 20(16), 1908-1917.
12. M. N. Bhoi, M. A. Borad, N. K. Panchal, & H. D. Patel, *Int. Lett. Chem. Phys. Astron.*, **2015**, 53, 106-113.
13. M. N. Noolvi, H. M. Patel, and M Kaur, *European journal of medicinal chemistry.*, **2012**, 54, 447-462.
14. D. T. Ruijie, T. John, B. G. Harry, *J Med. Chem.*, **2016**, 59, 13.
15. Yoshikawa, T., Naito, Y., Tanigawa, T., Yoneta, T., and Kondo, M. *Biochim. Biophys. Acta.*, **1991**, 1115, 15-22.
16. Cho, C. H. *Drug Developm. Res.*, **1992**, 27, 61-65.
17. Furuta, S., Toyama, S., Miwa, M., Itabashi, T., Sano, H., and Yoneta, T. *Jpn. J. Pharmacol.*, **1995**, 67, 271-278.
18. U. C. Patil, M. C. Mandewale, B. R. Thorat and R. S. Yamgar, *Journal of Chemical and Pharmaceutical Research.*, **2015**, 7(8), 159-167.
19. R. Schwalbe, L. Steele-Moore and A. C. Goodwin, eds., Antimicrobial susceptibility testing protocols. Crc Press., **2007**.