*The Pharmaceutical and Chemical Journal*, 2016, 3(4):119-124

*Available online www.tpcj.org*

**Review Article**

**ISSN: 2349-7092**
**CODEN(USA): PCJHBA**

# Review Study on Metal Complexes Synthesized from Therapeutically Important Schiff Bases

**Suman Malik[1], Bharti Jain[2], Amar Sohail Mirza[1], Archana Singh[1]**

[1]Deptt.of Chemistry Sadhu Vaswani Autonomous College Bairagarh, Bhopal
[2]Department of Chemistry, SNGGPG College, Shivaji Nagar, Bhopal -462016, M.P., India

**Abstract** Schiff bases are the compounds which are mainly formed by the condensation of the aldehydes and amines. Benzothiazole is a privileged heterocyclic scaffold having a benzene ring fused with a five membered thiazole ring. A few Substituted 1, 3-benzothiazole derivatives are an important class of heterocyclic compounds. In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. Benzothiazole moiety is very small but it posses different biological activities. Not only benzothiazole but its different substituted derivatives also give different biological activities. Researches carried out on benzothiazole moiety had established promising antimicrobial activities like antimalarial, antifungal, anti tubercular, antiviral as well as antitumor, analgesic and anti-inflammatory activities.

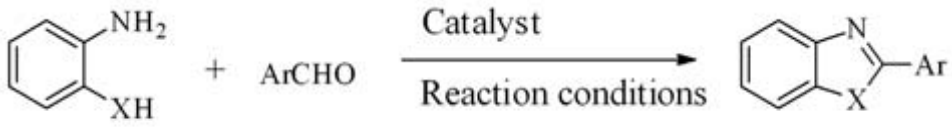
**Keywords** Benzothiazole, biological activities, Schiff base, heterocyclic compounds

## Introduction

Schiff bases are the condensation products of primary amines and carbonyl compounds and usually formed by the condensation of an aldehyde or ketone with primary amine [1]. Schiff base ligands are essential in the field of coordination chemistry, especially in the development of complexes of Schiff bases because these compounds are potentially capable of forming stable complexes with metal ions [2-3]. Schiff bases have very flexible and diverse structures [4]. Schiff bases are characterized by an imine group –N=CH-, which helps to clarify the mechanism of transamination and racemization reaction in biological system. It exhibits antibacterial and antifungal effect in their biological properties [5].Metal complexes possess a structure consisting of a central metal atom, bonded to a surrounding array of molecules or anions [6]. The advances in inorganic chemistry provide better opportunities to use metal complexes as therapeutic agents [7]. The study of the coordination of transition metal ions with different types of ligands has been amplified by the recent developments in the field of bioinorganic chemistry and medicines [8,9]. The rich diversity of transition metal coordination chemistry, therefore, provides exciting prospects for the design of novel coordination ligands having unique structures and valuable functional characteristics [10].

Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number of 2-amino benzothiazoles were intensively studied as central muscle relaxants [11]. Benzothiazoles are fused member rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole. The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole [12]. Moreover, benzothiazoles are present in a range of marine or terrestrial natural compounds that have useful biological activities. Benzothiazoles have been therapeutically useful in the treatment of various diseases such as neurodegenerative disorders, local brain ischemia and cancer [13]. Benzothiazole azo dyes are well established as mordant and disperse dyes. Azo dyes account for approximately 60-70% of all dyes used in food and textile

manufacture [14]. Benzothiazole nucleus has received much attention due to its diversified molecular design and remarkable optical and electronic properties [15]. Benzothiazole compounds containing different hetero atom, substituent have a tendency to form a good metal complexes and their substitute benzothiazole enhances on complex formation with suitable metal [16]. Hydrazino benzothiazoles and acetanilide derivatives from an important class of medicinal compounds. Compounds containing a hydrazino benzothiazole, hydrazino benzothiazine and substituted chloro acetanilide components have shown a broad spectrum of chemotherapeutic properties [17]. Microwave–assisted organic synthesis (MAOS) has been widely employed to enable and expedite the synthesis of diverse heterocycles. Microwave irradiation has been shown not only to reduce reaction times, but also often to provide higher yields of the desired products as compared to traditional heating methods[18]. It was reported that the 2- and 5-substituted benzothiazole, benzoxazole and benzimidazole derivatives had antimicrobial activities against some Gram-positive, Gram negative bacteria and the yeast *Candida albicans* [19]. Several works have been carried out on the transition metal complexes of 2-substituted benzothiazole derivatives. Very less work is done on the synthesis of 2-substituted benzothiazoles and its transition metal complexes involving some amino acids and the efforts were taken for the synthesis, characterization and antimicrobial studies of transition metal complexes containing 2-substituted benzothiazole and amino acids [20]. Bezimidazole and benzothiazole derivatives show significant activities against various viruses such as human cytomegalovirus (HCMV), 1 herpes (HSV-1),2,3, HIV 4,5 influenza etc. The most commonly used method involves direct condensation of *o*-phenylene diamine or *o*-aminothiophenol with aldehyde to afford a Schiff base which then undergoes oxidative cyclisation to yield corresponding 2-substituted benzimidazoles or benzothiazoles [21].




X=NH
X=S

X=NH
X=S

**Related Work and Importance**

Neha *et al.* [22] have synthesized 2-amino-6-chlorobenzothiazole and 2-amino-6-methyl benzo- thiazole with copper (II) palmitate under microwave irradiation. It is observed that the enhanced activity of complexes is also due to synergistic mechanism, i.e. free ligand and pure soap show less activity but on complexation their activity was enhanced. Hiremath *et al.* [23] have derived some Schiff bases from 7-chloro-6-fluoro-2-aminobenzothiazole with substituted salicylalde- hydes and their transition metal complexes of Cu(II), Co(II), Ni(II), Zn(II), Cd(II) and Hg(II) and characterized them by elemental analysis, TGA and DTA studies. Their studies indicate the formation of 1:2 complexes of the type $ML_2(H_2O)_2$ and the spectral results indicate that, the ligands coordinate through azo-methine nitrogen and phenolic oxygen to the metal ions. S.M.Verma *et al.*[24] have synthesized benzothiazoles which are heterocyclic sulphonamides, heterocyclic guanidine and heterocyclic methoxy derivatives. They saw that a receptor is expressed in the brain, where its important role is to regulate the glutamate and dopamine release makes it's a potential therapeutic for the treatment of insomnia, pain, depression, drug addiction and Parkinson's disease. Ravindra *et al.* [25] have synthesized 2-amino-5 hydroxybenzothiazole and 6-hydroxy-3-methyl-1-1,2-benzisoxazole by treating 2-amino-5-hydroxybenzothiazole, and 6-hydroxy-3-methyl-1,2-benzisoxazole with dihaloalkane by using potassium carbonate as base. This synthesis shows a convenient synthesis of some unsymmetrical alkanes with good yield. K. Ravi *et al.* [26] have showed that the molecules with benzoxazoles, benzimidazoles, and benzothiazole portion are attractive targets for synthesis of various compound and they often exhibit diverse biological properties. They are effective against human cytomegalovirus and are also efficient neuropeptide Y Y1 receptor antagonists. Parvathy *et al.*[27] have studied that these eight benzothiazole derivatives {5[(1,3-benzothiazol-2-ylsulfanyl)methyl] 1,3,4-oxadiazol-2-yl}- benzoic acid, 4{5[(1,3-benzothiazol-2-ylsulfanyl) methyl]-1,3,4-oxadiazol-2-yl} aniline,-2 (1,3-benzothiazol-2-ylsulfanyl) *N*' [(*E*) (4-hydroxy-3-methoxyphenyl)

methylidene] acetohydrazide,-2 (1,3-benzothiazol-2-ylsulfanyl) *N*' [(*E*) (-2-hydroxyphenyl) methylidene] acetohydrazide and 2(1,3-benzothiazol-2-ylsulfanyl)*N*'[(*E*)furan-2yl- methyl- idene]acetohydrazide have highest docking score, lesser toxicity profile and a promising approach to improve therapeutic properties. F. Nourmohammadian [28] have synthesized series of dichromophoric dyes based on 2-aminobenzothiazoles and 3-amino-1,2,4 -triazole with high yields and these dyes have been classified as disperse dyes. These synthesized dyes could be used as an indicator for different solvents. Sanja *et al.*[29] have reported the preparation and properties of some copper(II), cobalt(II) and nickel(II) complexes with 2-amino- benzimidazole and the synthesized complexes are of the general formula: $[ML_2Cl_2]\cdot nH_2O$; M=Cu, Co or Ni; n=0 or 2). They compared higher activity of the some complexes with free ligands, by using chelation theory. This theory explains that the decrease in the polarizability of the metal could enhance by lipophilicity of the complexes. N. Siva *et al.*[30] have prepared 4-thiazolidinones which are hetaryl- substituted at the 2-position by the reaction of mercaptoacetic acid with aldimines. This prepared complexes shows appreciable activity with standard drugs at same concentration. Sachin *et al.* [31] have prepared of 3-aryl-1-(7-chloro-6-fluoro-1-benzo- thiazole-2yl) pyrazole derivative from the Schiff bases of aromatic ketones with dimethyl- formamide and phosphorous oxychloride. Their results show that nature of substituent and substitution pattern on the benzene ring may have a considerable impact on antibacterial and antifungal activities. Xiao-Feng *et al.*[32] have prepared 1,2-phenylenediamine, 2-aminophenol, and 2 aminothio- phenol by oxidative cyclization with pyridine carboxaldehydes and affords the benzimidazole, benzoxazole, and benzothiazole pyridyl ligands. This area will investigate the cytotoxicities of such complexes against cisplatin-sensitive and cisplatin-resistant cells and the results of which will be published in due course. K. K. Sivakumar *et al.* [33] have studied the synthesis of only 12 Schiff bases of 5-amino-4-[2-(4-nitro-1,3-benzothiazol-2 yl) hydrazinyli- dene]- 2,4-dihydro-3*H*-pyrazol-3-one. All the synthesized compounds showed mild to moderate activity against gram-positive bacteria and also more potent against gram-negative bacteria. Pranav *et al.*[34] have synthesized *o*-phenylenediamine or *o*-aminothiophenol by direct condensation with aldehyde to afford a Schiff base which undergoes oxidative cyclisation to yield corresponding 2-subtituted benzimidazoles or benzothiazoles. Their simple workup procedures and easy availability of the reagents make this route more attractive and economi- cally viable. T.Narasaiah *et al.* [35] have synthesized urea/thiourea derivatives by the reaction of equimolar quantities of 2-(benzo[d]thiazol-2-yl) aniline in dry tetrahydrofuran and various isocyanates and thioisocyanates at room temperature in the presence of triethylamine with high yields. They concluded that the synthesized thiourea derivatives have shown potential antimicrobial activities against both gram positive and negative microbes at lower concentrations and the selected compounds were needed to be tested in animal models for their better pharma- cotherapy. Umarani *et al.* [36] have synthesized the selected title compounds by cyclizing 3-chloroaniline and potassium thiocyanate in presence of bromine that yield the corresponding 2-amino benzothiazole synthon, which on further treatment with different substituted aromatic aldehydes afforded Schiff bases. The phenyl ring of triazine bearing –OH and –OCH exhibited good biological activity and their predicted drug-likeness model score was found to be convince- ing among the series. Seetaramswamy *et al.* [37] have synthesized 2-amino benzothiazoles by reacting 4, 6-di substituted aniline with potassium thiocynate which on reaction with aromatic aldehyde formed Schiff base derivative and these compounds showed good anticancer activity against Hela cell lines. Shaikh Zeba *et al.* [38] have synthesized different heterocycle compound that are made by large number of efforts and their derivatives were found to posses antimicro- bial, anti-anthelmintic anti-convulsant, anti-diabetic, anti-tumor activities. Padmavathi *et al.* [39] have synthesized series of Schiff's base of several benzothiazole derivatives with para-nitro benzothiazole carboxylic acid by Jacobson synthesis. Then it furthur reduced to para amino benzothiazole carboxylic acid with ammonium chloride and iron metal. All these compounds have shown significant antibacterial activity with standard Ampicillin and Ketoconazole. Ranjana *et al.* [40] have synthesized new series of 2-amino-6-substituted benzothiazole by using 4-substituted aniline and potassium thiocyanate in presence of bromine in glacial acetic acid which further treated with various substituted aromatic aldehydes in presence of glacial acetic acid to get the 2-imino-benzothiazole derivatives. They concluded that the substitution of 6 position with fluoro, chloro, bromo and nitro groups at the terminal benzothiazole ring is bene- ficial for anticonvulsant activity. V.A. Jagtap *et al.* [41] have synthesized some novel 3-[6fluoro-7'-substituted-(1,3)benzothiazol-2-yl]p-benzene sulphonamido-2-onitrobenzene (1,3) thiazolidin-4-

one by fluorobenzenes 2-substituted benzothiazoles prompted us to synthesize novel compounds in hope of getting potent biodynamic agents. This class of compounds certainly holds great promise towards good active leads in medicinal chemistry. Neelima Mishra *et al*. [42] have studied that the Schiff bases, having azomethine (RHC=N-R') group and their metal complexes are widely used for industrial purposes. A. Xavier *et al.* [43] have studied that the acylation of Schiff bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylation agent to the carbon-nitrogen double bond and the reactions of this type have been of good use in natural product synthesis. Wail Al Zoubi [44] have studied that Schiff bases are generally bi- or tridentate ligands capable of forming very stable complexes with transition metals. S. Arulmurugan *et al.* [45] have studied that the Schiff bases are versatile ligands which are synthesized from the condensation of primary amines with carbonyl groups. These compounds are very important in medicinal and pharmaceutical fields. Abirami M *et al*. [46] have prepared a series of Cu(II) complexes from salicyldimine with acetate of Copper in water medium at room temperature and the Schiff base Cu(II) complexes have good biological activity against all tested bacteria and fungi. Ajay R. Patil *et al.* [47] have studied that the Schiff base and its mixed ligand complexes, in general, were non-hygroscopic and stable solids. These compounds were subjected to simultaneous thermo-gravimetric analysis to study their decomposition mechanism and thermal stability. Sunil Kumar Tobriya [48] have studied that the Schiff bases play an important role in Inorganic chemistry due to formation of very stable complexes with various transition and innertransition metals and it provide potential sites for bio-chemically active compounds. P. Anand *et al.* [49] have studied that the Schiff bases derived from various heterocyclic compounds displayed broad range of biological activities such as anticancer, antiviral, antimicrobial, anticonvulsant, antidepressant, angiotension-II receptor antagonist, anti-inflammatory and anti-glycation activity. In the year 1950, a number of 2-aminobenzothiazoles were intensively studied, as the 2-amino benzothia- zole scaffold is one of privileged structure in medicinal chemistry and reported cytotoxic on cancer cells [50].

## Conclusion

From the above review, it is clear that Schiff bases containing benzothiozole and its metal complexes showed variable toxicity against different bacteria. This research work was oriented towards the finding of newer derivatives of benzothiazole with enhance anti-inflammatory and analgesic activities. Drug discovery is a challenging process due to complexity of biological system. All the newly synthesized schiff base derivatives of benzothiazole were analysed with different spectral techniques and screened *in vitro* for their antibacterial activity against both Gram-positive and Gram-negative strains of bacteria and also subjected for the antifungal activity. Simple reaction conditions, simple workup procedures and easy availability of the reagents make this route more attractive and economically viable.

## References

1. Ashraf M. A, Mahmood K, Wajid A. IPCBEE, (2011), Vol. 10, pp 1–7.
2. Singh P., Singh Archana, Singh V. and Chauhan K.B.S. published in Oriental Journal of Chemistry, (2000), vol.16 (I), 165-167.
3. Souza P., Garcia-Vazquez J. A., Masaguer J. R, Transition Met. Chem., (1985), Vol. 10, pp 410.
4. C. Imrie, P. Kleyi, V. O. Nyamori, T. I. A. Gerber, D. C. Levendis, J. Look, J. Organomet. Chem., (2007), pp 692-3443.
5. Golcu A., Tumer M., Demirelli H., Wheatley R. Inorg. Chim. Acta, (2005), Vol. 358, pp 1785-1797
6. Cox, PA. Instant Notes Inorganic Chemistry. 2nd Edition. BIOS Scientific Publishers, New York, USA. (2005), pp 237.
7. Hariprasath, K, Deepthi, B, Sudheer, I. Babu, P. Venkatesh, P. Sharfudeen, S. Soumya, VJ. Chem. Pharm. Res. (2010),Vol. 2, pp 496-499
8. Suman Malik, Archana Singh and Nayaz Ahmed; J. of Applicable Chemistry, (2015), 4 (5): 1486-1491.
9. S. Z. Vatsadze, V. N. Nuriev and N. V. Zyk. Heterocycl. Compd., (2005). Vol. 41:9, pp 1091-1101.
10. Suman Malik, Suparna Ghosh and Liviu Mitu; published in J. Serb. Chem. Soc., (2000), 76(10) 1387-1394.

11. Jitender K Malik, F. V. Manvi, B. K. Nanjwade, Sanjiv Singh, Pankaj Purohit, Der Pharmacia Lettre (2010), Vol. 2 (1), pp 347-359.
12. Shiwani Jaiswal, Abhinav Prasoon Mishra, Ashish Srivastava, Research Journal of Pharmaceutical, Biological and Chemical Sciences, (2012), Vol. 3, pp 631-641.
13. Rupinder K. Gill, Ravindra K. Rawal, and Jitender Bariwal, Arch. Pharm. Chem. Life Sci. (2015), Vol. 348, pp 155–178.
14. Awale A. G, Gholse S. B, and Utale P.S, Research Journal of Chemical Sciences, (2013), Vol. 3(10), pp 81-87.
15. Abhay Kumar Verma, Alex Martin, Arun Kumar Singh, Indian J. Pharm. Biol. Res, (2014), Vol. 2(3), pp 84-89.
16. Mahasin F. Alias, Ameena N. Seewan, Diyala Journal for Pure Science, (2013), Vol. 9, pp 93-103.
17. Ch Suresh, J Venkateshwar Rao, K N Jayaveera, G Jayapal Reddy, International Journal of Pharmacy and Biological Sciences, (2011), Vol. 1, pp 409-413.
18. Sunder Singh, Praveen Sharma, Akash Yadav, C. T. Muttu, V. Ranjeeta, The Pharma Research Year, (2009), Vol. 1, pp 192-198.
19. Jitendra Shukla, Kuntal Hazra, P. Rashmi, L.V.G. Nargund, Der Chemica Sinica, (2011), Vol. 2, pp 4-10.
20. J Das J, RV Moquin, C Liu, AM Doweyko, HF Defex, Q Fang, S Pang, S Pitt, DR Shen, GL Schiever, JC Barrish, Bioorg Med Chem Lett. (2003), Vol. 13, pp 2587.
21. Pranav S. Chandrachood, Dinesh R. Garud, Tushar V. Gadakari,Rasika C. Torane, Nirmala R. Deshpande and Rajashree V. Kashalkar, Acta Chim. Slov. (2011), Vol. 58, pp 367–371.
22. Neha Mathur, Imran Ahmad, Ashok Kasana, Sonlata Bargotya and Biplab Manna. Inter -national Archive of Applied Sciences and Technology. (2014) Vol. 5, pp 37-42.
23. Hiremath Suresha Babu, T. Suresh, Suresh, D. Kotresh, and Shivaraj. International Journal of Pharmacy & Life Sciences. (2015) Vol. 6, pp 4708-4718.
24. S.M.Verma, Mohit Dadheech and Ram Pal Meena Journal of Pharma SciTech, (2012), Vol. 1, pp 30-35.
25. Ravindra M Kumbhar & V N Ingle, Indian Journal of Chemistry. (2009), Vol. 48, pp 996-1000.
26. K. Ravi Kumar, P. V. V. Satyanarayana, and B. Srinivasa Reddy, Hindawawi Publishing Corporation Journal of Chemistry(2013). pp 1110-1120.
27. Parvathy N.G, Manju Prathap, Mukesh. M and Leena Thomas, International Journal of Pharmacy and Pharmaceutical Sciences. (2013) Vol 5, Issue 2, pp 101-106.
28. F. Nourmohammadian, Progress in Colour, Colorants and Coatings. (2013), Vol. 6, pp 37-39.
29. Sanja O. Podunavac-Kuzmanović, Ljiljana Vojinović, Dragoljub M. Cvetković, ISIRR (2003), pp 197-202.
30. N. Siva Subramanian, G. Omprakash, Y. Anjaneyulu, V. R. M. Gupta and M. Ramadevi, Int. J. Chem. Sci. (2009) Vol. 7, No 3, pp 1537-1552.
31. Sachin G. Lokapure, B. Shivakumar and N. V. Kalyane, Scholars Research Library: (2013) Vol. 5, No 3, pp 21-26.
32. Xiao-Feng He, Christopher M. Vogels, Andreas Decken, Stephen A. Westcott, Science Direct. (2004) Vol.23, pp 155-160.
33. K.K. Sivakumar, G. Rajalakshmi and A. Rajasekaran, International Journal of Drug Design and Discovery. (2012) Vol. 3, Issue 4, pp 886-897.
34. Pranav S. Chandrachood, Dinesh R. Garud, Tushar V. Gadakari, Rasika C. Torane, Nirmala R. Deshpande and Rajashree V. Kashalkar, Acta Chim. Slov, (2011) Vol. 58, pp 367–371.
35. T. Narasaiah, C. Nagaraju, Indo American Journal of Pharmaceutical Sciences. (2015) Vol 2, Issue 3, pp 714-721.
36. Umarani N, Ilango K, Valentina P and Ishwarya T, Indian Journal of Pharmaceutical Education and Research. (2012) Vol. 46, Issue 4, pp 366-371.
37. Seetaramswamy S, Sekar V, Gandhimathi S, Laxmanadoss Murugesan, Perumal P International Journal of Current Pharmaceutical Research, (2013) Vol. 5, Issue 2, pp 63,64.

38. Shaikh Zeba K. Hisamoddin, Sanchaity Priyanka, Sharma Prachi Yogesh, Patel Nilam U, An International Journal of Pharmaceutical Sciences, (2014) Vol. 5, pp 207-225.
39. Padmavathi P. Prabhu, Sushant Pande, C.S.Shastry, International Journal of ChemTech Research, (2011) Vol. 3, No.1, pp 185-191.
40. Ranjana Singh and Suruchi Sharma, International Journal of Pharma Sciences and Research, (2014) Vol. 5 No 05, pp 213-217.
41. V. A. Jagtap, E. Jaychandran, G. M. Sreenivasa and B. S. Sathe, International Journal of Pharma and Bio Sciences, (2010) Vol.1, Issue-4, pp 484-490.
42. Neelima Mishra, Kavitan Poonia and Dinesh Kumar, International Journal of Advance- ments in Research & Technology, (2013) Vol. 2, Issue 8, pp 52-66.
43. Dr. A. Xavier and N. Srividhya IOSR Journal of Applied Chemistry, (2014) Vol.7, Issue 11, pp 06-15.
44. Wail Al Zoubi, International Journal of Organic Chemistry, (2013) Vol. 3, pp 73-95.
45. S. Arulmurugan, Helen P. Kavitha and B.R. Venkatraman, Rasayan J. Chem, (2010), Vol. 3, No. 3, pp 385-410.
46. Abirami M and Nadaraj V, Journal of Chemical and Pharmaceutical Sciences, (2014), Vol. 7, Issue 2, Pp 103-108.
47. Ajay R. Patil, Kamini J. Donde, Sambhaji S. Raut, Vishwanath R. Patil and Rama S. Lokhande. Journal of Chemical and Pharmaceutical Research, (2012) Vol. 4(2), pp 1413-1425.
48. Sunil Kumar Tobriya, International Journal of Science and Research, (2014) Vol. 3, Issue 9, pp 1254-1257.
49. P. Anand, V.M. Patil1, V.K. Sharma, R.L. Khosa, N. Masand, International Journal of Drug Design and Discovery, (2012) Vol. 3, Issue 3, pp 851-868.
50. Wang M, Gao M, Mock B, Miller K, Sledge G, Hutchins G, Zheng Q.Bioorg Med Chem. (2006), Vol. 14, pp 8599-8607.