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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF Cu (II) COMPLEXES OF SOME NOVEL 4-(5-METHYL-1*H*-TETRAZOL-1-YL) SCHIFF BASE LIGANDS

[1]Rajkumar G. Momle, [2]Suresh G. Vedpathak, [3]Gopal K. Kakade*

[1]Late Shankarrao Gutte ACS College Dharmapuri, 431 515 (MH) India
[2]Department of Chemistry, S. M. Dnyandeo Mohekar College, Kalamb, 413 507 (MH), India
[3]Department of Chemistry, MSP Mandal's ASC College, Kille-Dharur, 431 124 (MH), India

Abstract : This study has been undertaken to investigate the synthesis of Cu (II) complexes from novel Schiff bases prepared by reacting 5-methyl-1*H*-tetrazol-1-yl substituted anilines with salicyaldehyde and 5-bromo-2-hydroxybenzaldehyde in hot alcoholic solution. The complexes were subjected for their antibacterial screening where the activity of Cu (II) complexes **4a** and **4b** against *S. typhi* with MIC 26 mm were found more potent than standard drug tetracycline (21 mm) while other complexes have shown comparable antibacterial activity at the same concentration. Antifungal activity of the ligands has enhanced on complexation with Cu (II) metal where complexes **4a** and **4b** shows potent antifungal activity against *S. cerevisiae* and *A. niger* than the other complexes.

Keywords : Antibacterial activity, Antifungal activity, Cu (II) complexes, Schiff bases, Tetrazole.

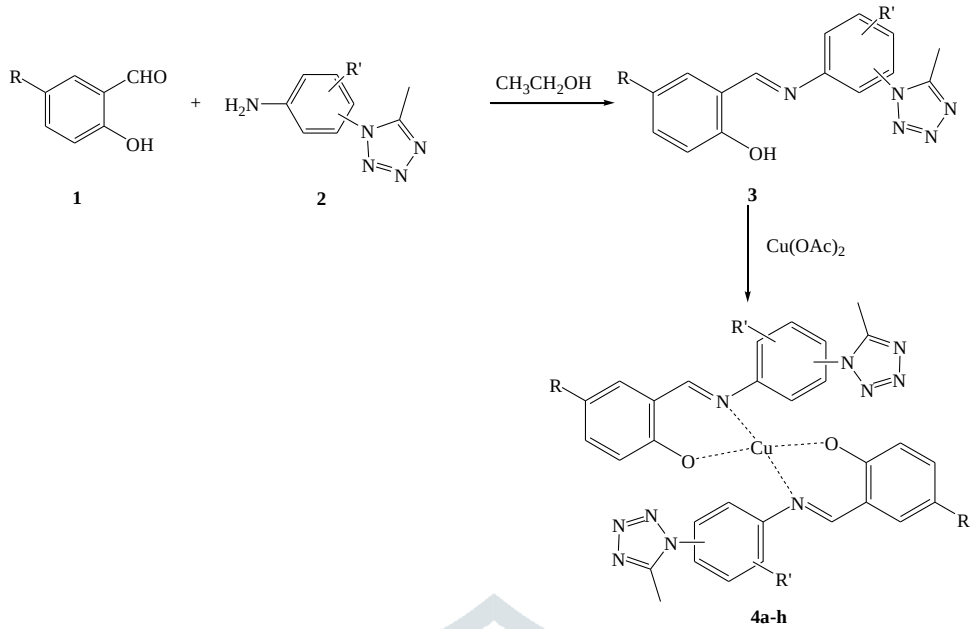
I. INTRODUCTION

Multidrug-resistant (MDR) bacteria, a group of frequent causative pathogens in healthcare, are typically associated with nosocomial infections often cause complex illnesses, mainly respiratory, ocular, urinary track, endocarditis, bone and joint, and skin, etc. These infections are tricky to treat, kind of antibiotics used which lead to the emergence of new mutant strains having high resistance to many antibiotics.[1] Hence much attention has been given on the development of new drugs with enhanced antimicrobial activity.

Recently, the tetrazole conjugates have found to possess broad spectrum of antibacterial activity notably thieno[2,3-*d*] pyrimidines,[1] pyrrolo[3,2-*e*]pyrimidines,[2] quinoline,[3] quinoxalines,[4] thiazole,[5] etc. Consequently, tetrazole derivatives such as biphenyl tetrazoles,[6] triazolo[4,3-*d*]tetrazolo[5,1-*f*]-1,2,4-triazines[7] substituted aryl tetrazolo[1,5-*b*]1,2,5- oxadiazepin-9-ones[8] and 2-(5- substituted phenyl-1*H*-tetrazol-1-yl) pyridine[9] have been found to possess promising antibacterial activity. In search of new antimicrobial agents, we underwent the synthesis of new Schiff base ligands bearing tetrazole moiety and their Cu (II) complexes for their enhanced antibacterial and antifungal activities.

II. RESULT AND DISCUSSION

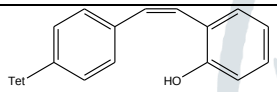
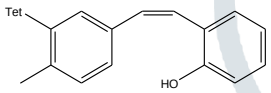
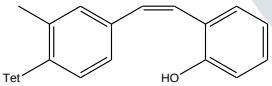
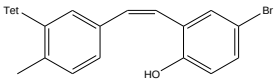
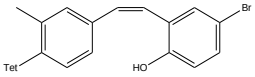
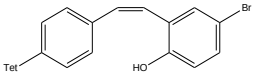
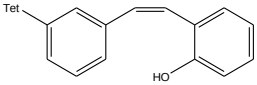
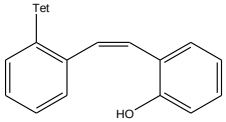
The reaction of salicyaldehyde and 5-bromo, 2-hydroxybenzaldehyde with 5-methyl-1*H*-tetrazol-1-yl substituted anilines in ethanol at room temperature resulted Schiff bases with excellent yields. The column purified Schiff base ligand was then refluxed in ethanol with $Cu(OAc)_2$ yields the resultant Cu(II) metal complexes (Scheme 1). The formation of coordination complex with Cu (II) metal was confirmed with the help sharp modification between the IR spectra of the metal complexes and the ligands.



Scheme 1. Synthesis of Cu (II) complexes

The *in vitro* antibacterial activity of the synthesised Cu (II) complexes have been tested against four gram negative bacterial pathogens *Enterobacter aerogenes, Pseudomonas aerogenosa, Salmonella typhi, Shigella boydii* and *Salmonella typhi* and two gram positive bacterial pathogens *Bacillus subtilis and Staphylococcus aureus.* The test solution was prepared in dimethylsulfoxide (DMSO) and Minimum Inhibitory Concentrations (MIC) was determined by means of disk diffusion method and the results are presented in **Table 1**. All the Cu (II) complexes exhibited much higher *in vitro* antibacterial activity than the parent ligand against all the bacterial pathogens.

Table 1. *In vitro* antibacterial activities of Schiff base metal complexes

Entry	Compound	Gram-negative bacteria				Gram-positive bacteria	
		Enterobacter aerogenes	*Pseudomonas aerogenosa*	*Salmonella typhi*	*Shigella boydii*	*Bacillus subtilis*	*Staphylococcus aureus*
4a		12	15	26	18	20	18
4b		12	13	26	20	18	22
4c		11	10	10	14	08	14
4d		24	09	20	18	18	04
4e		21	12	13	12	16	06
4f		18	07	17	14	13	06
4g		11	09	11	10	09	14
4h		13	08	14	12	11	16
Std.	**Tetracyclin**	20	33	21	26	25	30

*Tet. = 5-methyl-1*H*-tetrazol-1-yl

Complex **4a** and **4b** exhibited relatively more potent activity against *Salmonella typhi* (MIC- 26 mm) than the ligand **3a** and **3b** (MIC- 6 mm and 5 mm respectively) and standard drug tetracycline (MIC- 21 mm). Furthermore, both the complexes **4a** and **4b** showed pronounced activity against *Shigella boydii*, *Bacillus subtilis* and *Staphylococcus aureus.* The complex **4d** showed

significant activity against *Enterobacter aerogenes, Salmonella typhi, Shigella boydii* and *Bacillus subtilis*. Complex **4d** showed high activity towards *Shigella boydii*, while complexes **4e, 4f, 4g** and **4h** showed moderate activity toward tested pathogens.

Table 2. *In vitro* antifungal activity of Schiff base metal complexes

Compounds	*Candida albicans*	*Saccharomyces cerevisiae*	*Aspergillus niger*
4a	19	18	16
4b	15	20	22
4c	05	11	06
4d	22	12	15
4e	20	10	09
4f	17	10	13
4g	13	12	14
4h	13	14	10
Nystatin	25	20	30

The *in vitro* antifungal activity of Cu (II) complexes have been tested against *Candida albicans, Saccharomyces cerevisiae and Aspergillus niger*. The zones of inhibition (in mm) of the tested complexes are listed in Table 2. Complexes **4a**, **4b** and **4d** showed significant activity against *Candida albicans, Saccharomyces cerevisiae* and *Aspergillus niger*. Complex **4d** and **4e** showed promising activity against *Candida albicans* while other complexes were found to show moderate to less activity against tested fungal pathogens.

III. MATERIALS AND METHODS

All the chemicals were purchased from commercial suppliers. The melting points were determined in open capillaries using melting point apparatus (Model MP-96) and are uncorrected. The progress of reaction and purity of the product were monitored by thin layer chromatography. ^{1}H NMR was recorded using 400 MHz Varian Mercury plus 400 MHz FT NMR spectrometer in $CDCl_3$ and reported on δ scale in ppm, relative to TMS (δ = 0.00 ppm). IR spectra were recorded and reported in cm^{-1}.

Synthesis of Compound 3a-h: The compound 3a-h have been synthesized by using previously reported method.[14] To a solution of 4-(5-methyl-1*H*-tetrazol-1-yl)benzenamine (**2**) (1.2 g, 0.5 mmol) in 20 mL ethanol were added substituted aldehyde (**1**) (0.52 g, 0.5 mmol). The mixture was stirred at room temperature for 30 min. poured into water, filtered and dried. Column chromatography (4:1::hexane-EtOAc) gave Schiff base **3** (1.19 g, 95 %).

General method for the synthesis of Compound 4a-h: To a hot solution of Schiff base (**3**, 1 mmol) in 20 ml ethanol was added $Cu(OAc)_2$ (0.55 mmol). The mixture was stirred for 2 hrs. at 50-60ºC. The solution was then allowed to cool to room temperature and the solid formed was filtered, washed with ethanol and dried. (Yield 90 - 95 %)

IV. CONCLUSION

We have designed and synthesized Cu(II) complexes of a novel tetrazole bearing Schiff base ligand, and screened for their antibacterial and antifungal activities. The results revealed that all the complexes were found to exhibit enhanced antibacterial and antifungal activities than the ligand. Complex **4a** exhibited relatively more potent activity against *Salmonella typhi* (MIC- 26 mm) than the ligand (MIC-14 mm) and standard drug tetracycline (MIC- 21 mm). In addition, the complex **4a** showed promising activities against other bacterial pathogens. The results are favourable for further studies in emerging new trends of tetrazole bearing scaffolds as potential antimicrobials.

REFERENCES

[1] Salahuddin M.; Singh S.; Shantakumar S.M., *Rasayan J Chem.* **2009**; *2*(1), 167.
[2] Dave C.G.; Shah R.D., *Molecules*, **2002**, *7*, 554.
[3] Bekhit A.A.; El-Sayed O.A.; Elsayed A.; Park J.Y., *Eur. J. Med. Chem.*, **2004**, 39, 249.
[4] Natrajan U., *Der Pharma Chemica*, **2010**, 2(1), 159.
[5] Patil H.N.; Varadaraji D.; Suban S.S; Ramasamy V.R.; Kubendiran K., *Org. Commun.* **2010**, *3*, 45.
[6] Rao S.N.; Ravisankar T.; Latha J.; Sudhakar Babu K., *Der Pharma Chemica*, **2012,** *4*(3), 1093.
[7] Taha M.A.M.; El-Badry S.M., *J. Korean Chem. Soc.*, **2010,** *54*(4), 414.
[8] Taha M.A.M.; El-Badry S.M., *J. Korean Chem. Soc.*, **2011**, *55*(6), 974.
[9] George S.; Shanmugapandiyan P., *Int. J. Pharm. Sci.*, *4*(3) 104.
[10] Rao B.U.; Krishna V.; Rao G.N., *Asian J. Chem.*, **2015**, *27*(12), 4405.
[11] Chohan Z.H.; Supuran C.T.; Scozzafava A., *J. Enzyme Inhib. Med. Chem.*, **2004**, *19*, 79.
[12] Pavel N.G.; Sergei V.V.; Oleg A.I., Russ. Chem. Rev., **2006**, *75*, 507.
[13] Vedpathak S.G.; Momle R.G.; Kakade G.K.; Ingle V.S. *World J. Pharm. Res.*, 2016, *5*, 1049.
[14] Vedpathak S.G.; Kakade G.K.; Dixit P.P., Ingle V.S. *Asian J. Org. Med. Chem.* 2018, *3(3)*, 69.