Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(2):313-317
(http://derpharmachemica.com/archive.html)

Potent antimicrobial agents derived from combination of transition metal with sulfamethizole and phthalic anhydride

Hitesh R. Patel and Asha D. Patel*

Department of Chemistry, M. N. College, Visnagar

ABSTRACT

In the present study a novel 2-[{4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl}carbamoyl]benzoic acid (MTSPCB) was prepared by reaction of phthalic anhydride with Sulfamethizole. The prepared ligand was characterized by elemental analysis and spectral studies. The transition metal complexes viz. Cu^{2+}, Ni^{2+} , Co^{2+} , Mn^{2+} and Zn^{2+} of MTSPCB were prepared and characterized by metal-ligand (M:L) ratio, IR, reflectance spectroscopies and magnetic properties. All the prepared metal complexes and ligand were studies as antimicrobial agent. Among all the metal complexes, Zn^{2+} and Cu^{2+} metal complexes have shown significant activity.

Keywords: Phthalic anhydride, Sulfamethizole, Magnetic moment, Spectroscopic study and Antifungal properties.

INTRODUCTION

In inorganic chemistry most active research area is organometallic chemistry. Recently,We have already drawn attention [1–5] to coordination between metals or their complexes, and antibacterial [6–12], antitumour [13–15], and anticancer [16, 17] activities. Many in vivo studies have indicated [18–20] that biologically active compounds become more bacteriostatic and carcinostatic upon chelation. Such interaction of transition-metal ions with amino acids and peptides is of immense biological importance [21–23]. They are also effective for the treatment of urinary, intestine, and ophthalmic infections, scalds, ulcerative colitis [24], More recently, sulfonamides are used as an anticancer agent [25], as the antiviral HIV protease inhibitor amprenavir [26] and in Alzheimer's disease [27]. The reaction of phthalic anhydride derivatives with Sulfamethizole has not been reported for metal complaxation so far. Hence, it was thought that phthalic anhydride and Sulfamethizole moieties can put into one molecule frame may afford good biological active compound. The present article discuss about synthesizes, characterization and biological studies of 2-[{4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl}carbamoyl]benzoic acid (MTSPCB). Also its metal complexes based on literature serve regarding importance of complexes, it was thought to synthesis transition metal complexes of prepared ligand in order to improve in biological activity.

MATERIALS AND METHODS

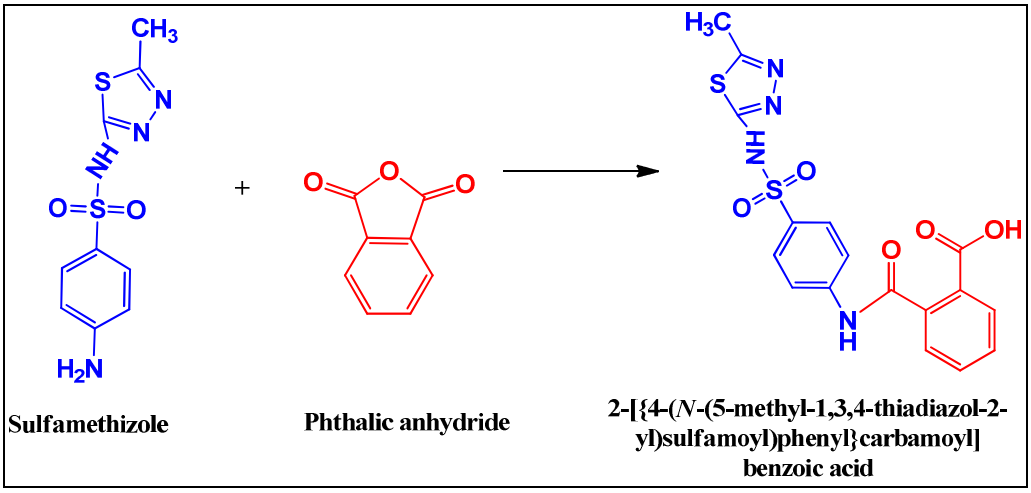
2.1. Materials and measurements

All the chemicals used were of laboratory grade received from Sigma–Aldrich. Sulfamethizole was taken direct purchase to Sigma–Aldrich. ^{1}H, ^{13}C and DEPT-135 NMR spectra were recorded in $CDCl_3$ at room temperature using a Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR Spectrometer, TMS was used as internal reference. IR spectra were recorded neat by ATR on a Thermo Nicolet iS50 FT–IR spectrometer and are

reported in cm^{-1}. HR–MS data were obtained in methanol, with Thermo Scientific Orbitrap Elite Mass spectrometer. The elemental contents were determined by Thermo Finigen Flash1101 EA (Itally) the metals were determined volumetrically by Vogel's method [28]. To a 100 mg chelate sample, each 1 ml of HCl, H_2SO_4 and $HClO_4$ were added and then 1 g of $NaClO_4$ was added. The mixture was evaporated to dryness and the resulting salt was dissolved in double distilled water and diluted to the mark. From this solution the metal content was determined by titration with standard EDTA solution. Magnetic susceptibility measurement of the synthesized complexes were carried out on Gouy Balance at room temperature. Mercury tetrathiocynatocobalate (II) $Hg[Co(NCS)_4]$ was used as a calibrant. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. Melting point is measured by open capillary method using Sigma Melting Point Apparatus.

2.2. Synthesis of 2-[{4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl}carbamoyl]benzoic acid (MTSPCB)

The reaction mixture of phthalic anhydride (0.01 mole) in ethanol and (0.01 mole) Sulfamethizole in ethanol was refluxed for 2-3 hrs. The resulting solid was washed with water, dried and recrystallized from MeOH. Yield: 74.52 %, M.P. (193-194°C) was measurement with open capillary method and it is uncorrected. IR (cm^{-1}): 2950-2850 (Ar C-C), 3450-3360 (CONH, NH_2), 3430, 1680 (COOH),1620-1680(C=C),2260-2210(C=N). ^{1}H- NMR(δ ppm, 500 MHz, CDCl3): 11.80 (s, 1H, COOH), 8.32 (s, 1H, NH), 7.71-7.98 (m, 4H, Ar-H), 6.51-6.92 (d, 2H, CH=CH), 3. ^{13}C MNR (δ ppm, 125 MHz, CDCl3): 173.00, 167.60, 142.70, 141.10, 135.30, 134.00, 132.00, 131.50, 129.40, 119.00,118.00,. DEPT-135 (δ ppm, 125 MHz, CDCl3): 129.40, 119.00, 118.00,.



Scheme 1 Synthesis of MTSPCB

2.3. Synthesis of metal complexes of 2-[{4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl} carbamoyl]benzoic acid (MTSPCB)

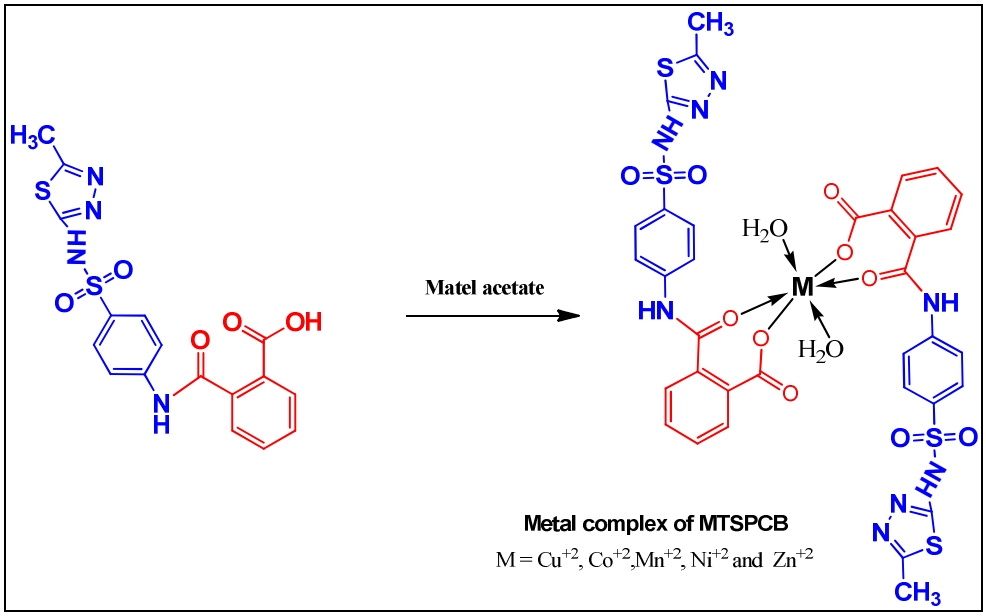
The metal complexes of MTSPCB with Cu^{2+}, Co^{2+}, Zn^{2+}, Mn^{2+}, and Ni^{2+} metal ions were prepared in two steps. All the metal complexes were prepared in an identical procedure.

Preparation of MTSPCB solution

The MTSPCB (0.05 mole) was taken in 100 ml beaker and formic acid (85% v/v) was added up to slurry formation. To this slurry water was added till the complete dissolution of MTSPCB. It was diluted to 20 ml.

Synthesis of MTSPCB -metal-complexes

In a solution of metal acetate (0.025 mole) in acetone: water (50:50 v/v) mixture (40 ml) the 20 ml of above mentioned MTSPCB solution (i.e. containing 0.05 M MTSPCB) was added with vigorous stirring at room temperature. The appropriate pH was adjusted by addition of sodium acetate for complete precipitation of metal chelate. The precipitates were digested on a boiling water bath and filtered off, washed by water and air-dried.



Scheme - 2 Synthesis of metal complexes of MTSPCB

Table 1. Analysis of MTSPCB ligand and its metal complexes

Empirical Formula	Yield (%)	Elemental Analysis									
		C%		H%		N%		S%		M%	
		Cald	Found	Cald	Found	Cald	Found	Cald	Found	Cald	Found
MTSPCB	75	48.80	48.75	3.37	3.30	13.39	13.33	15.33	15.20	-	-
$(MTSPCB)_2Cu^{2+}$	63	43.70	43.65	3.24	3.15	11.99	11.98	13.73	13.65	6.80	6.79
$(MTSPCB)_2Co^{2+}$	62	43.92	43.88	3.25	3.05	12.05	12.02	13.79	13.70	6.34	6.32
$(MTSPCB)_2Ni^{2+}$	64	43.93	43.87	3.25	3.01	12.05	12.01	13.80	13.65	6.31	6.30
$(MTSPCB)_2Mn^{2+}$	69	44.11	44.07	3.27	3.15	12.10	12.05	13.85	13.75	5.93	5.91
$(MTSPCB)_2Zn^{2+}$	65	43.62	43.45	3.23	3.20	11.97	11.90	13.70	13.68	6.98	6.95

2.4. Antibacterial activity

The synthesized compounds were screened for their antibacterial activities against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* at a concentration of 200 µg ml^{-1} in dimethylsulphoxide by agar diffusion method using streptomycin as standard. The minimum inhibitory concentrations (MIC) were detected by serial dilution method. The lowest concentration (µg ml^{-1}) of the compound, which inhibits the growth of bacteria maximum after 24 h inhibition at 37 ºC, was taken as MIC. The stock solution (10^{-2} M) was prepared by dissolving the complex in dimethylsulphoxide and the solutions were diluted to different concentrations in the same solvent in order to find the MIC values.

RESULTS AND DISCUSSION

The synthesis of 2-[{4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl}carbamoyl]benzoic acid (MTSPCB) was performed by a simple reaction of phthalic anhydride and Sulfamethizole. The resulted MTSPCB ligand was an amorphous brown powder. The C,H,N contents of MTSPCB (Table-1) are consistent with the structure predicted (**Scheme-1**). The IR spectrum of MTSPCB comprises the important bands of structure.

Table 2. Spectral features and magnetic moment of MTSPCB metal complexes

Metal Complexes	μ_{eff} (BM)	Electronic spectral data (cm^{-1})	Transition
MTSPCB-Cu^{2+}	2.51	23259 13177	Charge transfer $^2B_{1g} \rightarrow {}^2A_{1g}$
MTSPCB-Ni^{2+}	3.60	22566 15422	$^3A_{1g} \rightarrow {}^3T_{1g}(P)$ $^3A_{1g} \rightarrow {}^3T_{1g}(F)$
MTSPCB-Co^{2+}	4.75	23825 19165 8991	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$
MTSPCB-Mn^{2+}	5.60	23327 19153 16977	$^6A_{1g} \rightarrow {}^6A_{2g}\ {}^4E_g$ $^6A_{1g} \rightarrow {}^4T_{2g}$ (4G) $^6A_{1g} \rightarrow {}^4T_{1g}$(PG)
MTSPCB-Zn^{2+}	Diamag.	--------	---------

The broad band due to –OH group appeared at 3430 cm^{-1}. In this band the inflections are observed at 2970, 2930 and 2850cm^{-1}. The NMR spectrum of MTSPCB in DMSO indicates that the singlet of 1H at 11.8 δ ppm due to –COOH group. The aromatic protons are appeared in multiplicity at 7.7-7.9 δ. Thus the structure of MTSPCB is confirmed as shown in **Scheme - 1**.

The metal and C, H, N contents of metal complexes of MTSPCB (Table - 1) are also consistent with the predicted structure. The results show that the metal: ligand (M:L) ratio for all divalent metal chelate is 1:2.

Table 3. Antibacterial activity of MTSPCB ligand and its metal complexes

Sample	Zone of inhibition at 1000 ppm (%)			
	Escherichia coli	***Klebsiella pneumonia***	***Proteus vulgaris***	***Staphylococcus aureus***
MTSPCB	54	53	51	63
MTSPCB-Cu^{2+}	77	74	72	73
MTSPCB-Co^{2+}	62	68	71	68
MTSPCB-Ni^{2+}	58	67	63	64
MTSPCB-Mn^{2+}	62	59	61	63
MTSPCB-Zn^{2+}	76	73	62	74
Ampicillin	85	87	77	86

The infrared spectra of all the complexes are identical and suggest the formation of all the metalocyclic compound by the absence of band characteristic of free –OH group of parent MTSPCB. The other bands are almost at their respectable positions as appeared in the spectrum of parent- MTSPCB ligand. However, the band due to (M-O) band could not be detected as it may appear below the range of instrument used. The important IR Spectral data are shown in Table - 2.

Magnetic moments of metal complexes are given in Table - 2. The diffuse electronic spectrum of Cu^{2+} complexes shows two broad bands around 13177 and 23259 cm^{-1}. The first band may be due to a $^2B_{1g} \rightarrow {}^1A_{1g}$ transition. While the second band may be due to charge transfer. The first band shows structures suggesting a distorted octahedral structure for the Cu^{2+} metal complexes. The higher value of the magnetic moment of the Cu^{2+} chelate supports the same. The Co^{2+} metal chelate gives rise to two absorption bands at 23825 and 19165 cm^{-1}, which can be assigned $^4T_{1g} \rightarrow {}^2T_{2g}$, $^4T_{1g} \rightarrow {}^4T_{1g}(P)$transitions, respectively. These absorption bands and the μeff value indicate an octahedral configuration of the Co^{2+} metal chelate [29]. The spectrum of Mn^{2+} polymeric chelate comprised two bands at 19153cm^{-1} and 23377cm^{-1}. The latter does not have a very long tail. These bands may be assigned to $^6A_{1g} \rightarrow {}^4T_{2g(G)}$ and $^6A_{1g} \rightarrow {}^4A_{2g(G)}$ transitions, respectively. The high intensity of the bands suggests that they may have some charge transfer character. The magnetic moment is found to be lower than normal range. In the absence of low temperature measurement of magnetic moment it is difficult to attach any significance to this. The observed μeff values in the range 2.51-5.60 B.M are consistent with the above moiety [29].

The examination of antibacterial activity of ligand and it's all complexes (Table - 3) reveals that the ligand is moderately toxic against bacteria, while all the complexes are more toxic than ligand. Among all the complexes the Cu^{2+} chelate is more toxic against tested bacteria.

Acknowledgements
I am thankful to my guide, Dr.Asha D. Patel for their necessary some suggestion, providing valuable insights into seeing the whole paper. I am also thankfull to Principal of M.N.College,Visnagar for providing research facilities.

REFERENCES

[1] Chohan ZH, Praveen M, Ghaffar A. *Metal-Based Drugs.***1997**;4(5):267–272.
[2] Chohan ZH, Scozzafava A, Supuran CT. *Journal of Enzyme Inhibition and Medicinal Chemistry*. **2002**; 17(4):261–266.
[3] Chohan ZH, Kausar S. *Chemical and Pharmaceutical Bulletin.* **1993**;41(5):951–953.
[4] Ul-Hassan M, Chohan ZH, Scozzafava A, Supuran CT. *Journal ofEnzyme Inhibition and Medicinal Chemistry*. **2004**;19(3):263–267.
[5] Ul-Hassan M, Chohan ZH, Supuran CT. *Main Group Metal Chemistry*. **2002**;25(5):291296.
[6] Chohan ZH, Scozzafava A, Supuran CT. *Journal of Enzyme Inhibition and Medicinal Chemistry*. **2003**; 18(3):259–263.
[7] Seven MJ, Johnson LA. *Metal Binding in Medicine.* 4th ed.Philadelphia, Pa: Lippincott; **1960**.
[8]Srivastava RS. *Indian Journal of Chemistry*. **1990**;29A:1024.
[9] Patel VK, Vasanwala AM, Jejurkar CN. *Indian Journal of Chemistry.* **1989**;28A:719.
[10] Maggio F, Pellerito A, Pellerito L, Grimaudo S, Mansueto C, Vitturi R.
Applied OrganometallicChemistry. **1994**;8(1):71–85.
[11]Vitturi R, Mansueto C, Gianguzza A, Maggio F, PelleritoA, Pellerito L. *Applied Organometallic Chemistry*. **1994**; 8(6):509–515.
[12]Pellerito L, Maggio F, Consigilo A, Pellerito A, StoccoGC, Gremaudo S. *Applied Organometallic Chemistry*. **1995**;9(3):227–239.
[13] Vitturi R, Zava B, ColombaMS,PelleritoA,Maggio F, PelleritoL. *Applied Organometallic Chemistry.* **1995**;9(7):561–566.
[14] Rosenberg B, VanCamp L. *Cancer Research.* **1970**;30(6):1799–1802.
[15] Cleare MJ, Hoeschele JD. *Bioinorganic Chemistry.* **1973**;2(3):187–210.
[16] Narayanan VA, Nasr M, Paull KD. In: *Tin Based AntitumourDrugs.* Vol H 37. Berlin, Germany: Springer; **1990**: NATO ASISeries.
[17] Crowe AJ. The antitumour activity of tin compounds. In:*Metal Based Antitumour Drugs. Vol. 1*. London, UK: Freud;**1988**:103–149.
[18] Saxena AK. *Applied Organometallic Chemistry.* **1987**;1(1):39–56.
[19] Furst A. *The Chemistry of Chelation in Cancer.* 3rd ed. Springfield, Ill: Thomas; **1963**.
[20]Williams DR. *Journal of the Chemical Society. Dalton Transactions.* **1972**;(7):790–797.
[21] Jones AD, Williams DR. *Journal of the Chemical Society A.* **1971**:3159–3162.
[22] Pratt JM. *Inorganic Chemistry of Vitamin B12.* London, UK:Academic Press; **1972**.
[23] Shapiro SK, Schlenk F. *Transmethylation and MethionineBiosynthesis.* Chicago, Ill: University of Chicago Press; **1965**.
[24] Vullo D., De Luca V., Scozzafava A., CarginaleV., Rossi M., SupuranCT., Capasso C.: *Bioorg. & Med. Chem*., **2013**, 21, 4521
[25]Wilson C. O., Gisvold O., Block J. H.: *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 11th ed., Block J., Beale J. M., Eds., Lippincott Williams and Wilkins: Philadelphia, **2004**.
[26]Levin J. I., Chen J. M., Du M. T., Nelson F. C., Killar L. M., Skala S., Sung A., Jin G., Cowling R., Barone D., March C. J., Mohler K. M., Black R. A., Skotnicki J. S.: *Bioorg. & Med. Chem. Lett.* **2002**, 12, 1199.
[27]Kim D.-K., Lee J. Y., Lee N., Ryu D. H., Kim J.-S., Lee S., Choi J.-Y., Ryu J.-H., Kim N.-H., Im G.-J., Choi W.-S., Kim T.-K.: *Bioorg. & Med. Chem.* **2001**, 9, 3013.
[28]Hu B., Ellingboe J., Han S., Largis E., Lim K., Malamas M., Mulvey R., Niu C., Oliphant A., Pelletier J., Singanallore T., Sum F.-W., Tillett J., Wong V.: *Agonists. Bioorg. & Med. Chem.* **2001**, 8, 2045.
[29]B.R.Patil, *Oriental J. Chem*., **2006**, 18, 547.