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DESIGN, SYNTHESIS AND *IN-VITRO* ANTIMICROBIAL EVALUATION OF MANNICH BASE METAL COMPLEXES

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ABSTRACT: Succinimide and its derivatives are important substitutes of many medicinal compounds in the pharmaceutical field. One of the essential objectives in heterocyclic and medicinal chemistry is the synthesis of molecules having importance as therapeutic agents. Heterocyclic compounds and their derivatives contain an imide ring that can easily cross biological membranes *in-vivo*. Mannich reactions are one of the fundamental methods of C-C bond forming reactions in organic synthesis and withstand a diversity of functional groups. In view of this, the Mannich base1-((2,5-dioxopyrrolidin-1-yl)phenyl)methyl)thiourea and a few of its transition metal complexes with Mn(II) and Co(II) have been synthesized. The newly synthesized ligand and its metal complexes have been characterized by elemental analysis, molar conductance and FT-IR, UV-Visible NMR, Mass spectral studies, and magnetic measurements. The ligand and the corresponding metal complexes were screened for their antibacterial and antifungal activities. The metal complexes have shown marked activity against selected microorganisms than the ligand.

INTRODUCTION: The chemistry of coordination compounds comprises an area of chemistry that spans the entire spectrum from theoretical work on bonding to the synthesis of organometallic compounds. Some of the important types of coordination compounds occurs in biological systems. The use and significance of inorganic compounds have been invaluable to the medical field. Coordination compounds are found in many biomolecules as essential ingredients for the active site of enzymes. It is estimated that approximately half of all proteins contain a metal.

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Metallo-enzymes have one feature in common that the metal ion is bound to protein with one labile coordination site. This aspect of their coordination chemistry allows them to perform essential functions within the body. Thus, metalloproteins have many different functions in their cells, such as transport and storage of proteins and signal transduction proteins [1-7]. Mannich reaction affords a suitable method to introduce aminoalkyl substituent into a molecule.

In several instances, the Mannich derivatives exhibit better activity than the corresponding parent analogues *vide infra*. Succinimide derivatives are a part of a wide range of active molecules possessing CNS depressant [8], muscle relaxant [9], antitubercular [10], hypotensive [11], antibacterial [12], antitumor [13], antifungal [14], anticonvulsant [15] activities, *etc*. This work focuses on the synthesis of Mn(II) and Co(II) metal complexes of Mannich base derived from succinimide. The characterization studies of all the metal complexes have been done with appropriate methods. The ligand and the metal complexes were screened for anti-bacterial and anti-fungal activities.

MATERIALS AND METHODS: All the reagents were purchased in the highest quality available and were used without further purification. The solvents used in the synthesis were of analar grade obtained from commercial suppliers.

Physical Measurements: Elemental analysis was performed using Carlo Erba 1108 analyzer and Coleman N analyzer and was found within ± 0.5%. The molar conductivities of the metal complexes were measured in approximately 10^{-3}mol ethanol solution using a Systronics direct reading digital conductivity meter-304 with dip type conductivity cell. The IR spectra were recorded as KBr pellets on Perkin- Elmer 1000 unit instrument. Absorbance in the UV-Visible region was recorded in DMF solution using UV-Visible spectrometer. The ^{1}H & ^{13}C NMR of the Ligand was recorded on a Bruker instrument employing TMS as an internal reference and DMSO - DMF as solvent. The mass spectral study of the Ligand was carried out using LC mass spectrometer. Magnetic susceptibility measurements at room temperature were made by using a Guoy magnetic balance.

Preparation of Mannich base 1-((2,5-dioxopyrrolidin-1-yl)phenyl) Methyl) Thiourea (SBT): An aqueous solution of succinimide (0.01 mol) containing a known amount of thiourea (0.01 mol) was taken in a round-bottomed flask and fitted with a reflux condenser and a dropping funnel. While heating in a water bath, about 0.01 mol of benzaldehyde was added in drops, and the mixture is heated for an hour. Then the contents were transferred into the beaker after cooling and stirred with a magnetic stirrer for about 6 h. The beaker was taken out, and the contents were shaken occasionally. After two weeks, a solid product was obtained. It was filtered and recrystallized from methanol **Fig. 1**.

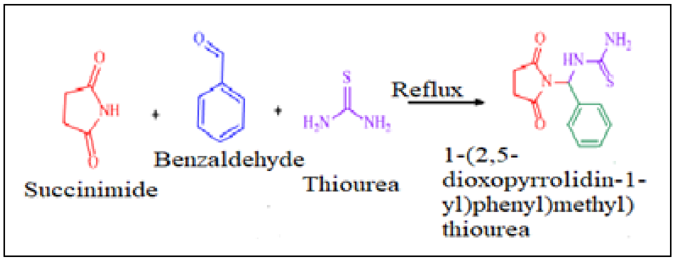

FIG. 1: PREPARATION OF MANNICH BASE 1-((2,5-DIOXOPYRROLIDIN-1-YL)PHENYL) METHYL) THIOUREA (SBT)

Reaction Scheme:

Synthesis of Manganous Chloride Complex of SBT: About 0.08 g (3 mmol) of Manganous chloride aqueous solution is taken in a 50 ml beaker. To this, about 0.1 g (3 mmol) of Mannich base SBT dissolved in ethanolic solution is slowly added and stirred well to obtain a clear solution and kept aside for 10 days. A resulting dull-white solid formed was separated and washed with methanol and dried in vacuum **Fig. 2**.

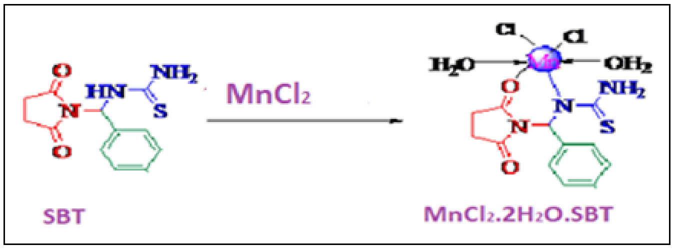

FIG. 2: MANGANOUS CHLORIDE COMPLEX OF SBT

Synthesis of Manganous Sulphate Complex of SBT: The Manganous sulphate complex of SBT was prepared slow addition of ethanolic solution of Mannich base SBT (0.1g, 3 mmol) to the ethanolic solution of Manganous sulphate (0.08 g, 3 mmol) with continuous stirring. The mixture is kept aside for about 10-14 days. After slow evaporation, a white-colored compound obtained was filtered and washed with methanol and dried in vacuum **Fig. 3**.

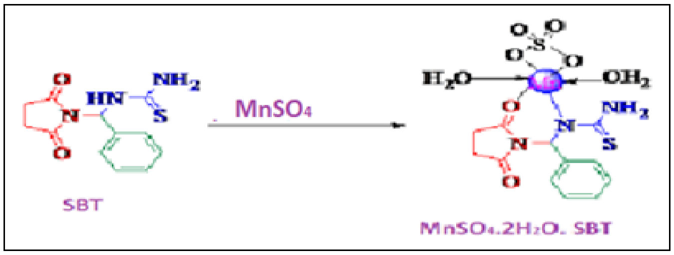

FIG. 3: MANGANOUS SULPHATE COMPLEX OF SBT

Synthesis of Cobalt Chloride Complex of SBT: The Cobalt chloride complex of SBT was prepared by slow addition of ethanolic solution of Mannich base SBT (0.1g, 3mmol) on the aqueous solution of cobalt chloride (0.8g, 3mmol) with constant stirring for 1 h and by keeping the contents aside for about 10 days for slow evaporation. It was observed that after 10 days, light blue crystals of the complex were formed. The compound was filtered and washed with methanol and dried in vacuum **Fig. 4**.

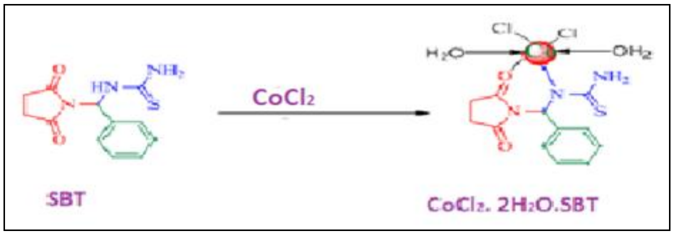

FIG. 4: COBALT CHLORIDE COMPLEX OF SBT

Synthesis of Cobalt Sulphate Complex of SBT: To an aqueous solution of 0.08 g (3 mmol) of Cobalt sulphate, 0.1g (3 mmol) of Mannich base SBT was slowly added with constant stirring. The content was allowed for slow evaporation for about 10 days. Blue crystals of the cobalt sulphate complex were formed in the solution, and the product was filtered, washed with methanol, and dried in a vacuum **Fig. 5**.

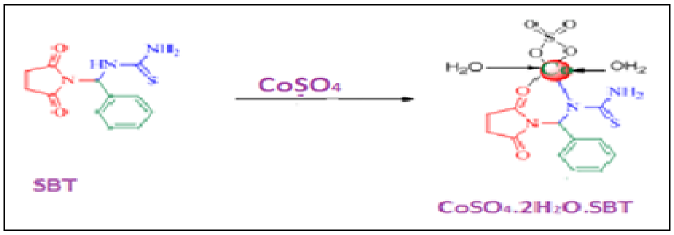

FIG. 5: COBALT SULPHATE COMPLEX OF SBT

RESULTS AND DISCUSSION:

Physical Measurements: The physical properties and elemental analysis of the prepared Ligand and their metal complexes are described in **Table 1**. The structures of metal complexes were further confirmed by conductivity measurements and magnetic moment determinations **Table 1**.

UV-Vis Spectroscopic Studies: The Manganous chloride complex shows four absorption bands at 18050 cm^{-1}, 24985cm^{-1}, 29125 cm^{-1} and 31272 cm^{-1} for the transitions $^6A_{1g}\rightarrow{}^4T_{1g}$, $^6A_{1g}\rightarrow{}^4E_{2g}$, $^6A_{1g}\rightarrow{}^4E_{1g}$ and charge transfer transitions, respectively. The μ_{eff} value was found to be 4.85B.M suggestive of high spin octahedral geometry [16-19].

The electronic spectra of Manganous sulphate complex exhibit absorption bands at 18021 cm^{-1}, 24967 cm^{-1} and 28305 cm^{-1} due to $^6A_{1g}\rightarrow{}^4T_{1g}$, $^6A_{1g}\rightarrow{}^4E_g+{}^4A_{1g}$ and $^6A_{1g}\rightarrow{}^4T_{2g}$ transitions respectively.

This spectral features [20-23] indicate octahedral geometry and is further supported by the observed magnetic moment values at 5.31B.M.

The Cobalt chloride complex registers four absorption bands at 6703 cm^{-1}, 14365 cm^{-1}, 18742 cm^{-1} and 29066 cm^{-1} due to $^4T_{1g}\rightarrow{}^4T2_g$, $^4T_{1g}\rightarrow{}^4A_{2g}$, $^4A_1g\rightarrow{}^4T_{1g}$ and charge transfer transitions respectively. The μ_{eff} value was found at 4.48 B.M suggesting octahedral geometry [24].

For the Cobalt sulphate complex the spectra appears at 6940 cm^{-1}, 14980 cm^{-1}, 18572 cm^{-1} and 24048 cm^{-1} due to $^4A_2\rightarrow{}^4T_2$, $^4A_2\rightarrow{}^4T_1$, $^4T_{1g}\rightarrow{}^4T_{2g}$ and CT transitions respectively. The μ_{eff} value was found to be 5.08 B.M in agreement with octahedral geometry [25] **Table 1**.

TABLE 1: ANALYTICAL DATA & UV SPECTRAL DATA OF THE LIGAND SBT & ITS METAL COMPLEXES

Compound	C	H	N	O	Λm (ohm^{-1} cm^2 mol^{-1}) & μ_{eff} (B.M)	λ_{max} (cm^{-1})	Transition Assignment	Geometry
SBT($C_{12}H_{12}N_3O_2S$)	50.10	5.04	14.23	16.28	-	-	-	
	(50.08)	(5.00)	(14.20)	(16.26)				-
$MnCl_2.2H_2O$.SBT	33.28	3.93	8.76	16.65	42	18050	$^6A_{1g}\rightarrow{}^4T_{1g}$	High spin
($C_{12}H_{16}Cl_2N_3MnO_4S$)	(33.24)					24985	$^6A_{1g}\rightarrow{}^4E_{2g}$	Octahedral
		(3.90)	(8.74)	(16.63)	(4..85)	29125	$^6A_{1g}\rightarrow{}^6E_{1g}$	
						31272	CT	
$MnSO_4.2H_2O$.SBT	35.22	3.04	8.35	22.46	45	18021	$^6A_{1g}\rightarrow{}^4T_{1g}$	Octahedral
($C_{12}H_{16}N_3MnO_8S_2$)	(35.20)					24967	$^6A_{1g}\rightarrow{}^4E_g+{}^4A_{1g}$	
		(3.02)	(8.37)	(22.45)	(5.31)	28305	CT	
$CoCl_2.2H_2O$.SBT	34.15	3.99	8.64	16.73	44.5	6703	$^4T_{1g}\rightarrow{}^4T_{2g}$	Octahedral
($C_{12}H_{16}Cl_2CoN_3O_4S$)	(34.17)					14365	$^4T_{1g}\rightarrow{}^4A_{2g}$	
		(3.98)	(8.61)	(16.72)	(4.48)	18742	$^4A_{1g}\rightarrow{}^4T_{og}$	
						29066	CT	
$CoSO_4.2H_2O$.SBT	35.90	3.04	8.93	23.86	67	6940	$^4A_2\rightarrow{}^4T_2$	Octahedral
($C_{12}H_{16}CoN_3O_8S_2$)						14980	$^4A_2\rightarrow{}^4T_1$	
	(35.88)	(3.02)	(8.91)	(23.84)	(5.08)	18572	$^4T_{1g}\rightarrow{}^4T_{2g}$	
						24048	CT	

IR Spectral Analysis of LIGAND and its Metal Complexes: In order to study the binding mode of the Ligand to metal in the complexes, the IR spectrum of the free Ligand was compared with the corresponding metal complexes. Selected vibrational bands of the Ligand and its metal complexes and their assignments are listed in **Table 2**. The IR spectrum the free Ligand exhibited a strong band at 1681 cm^{-1} which could be assigned to $\nu_{C=O}$ of the succinimide ring. A band around 3285 cm^{-1} could be attributed to stretching vibration of $\nu_{N=H}$ bond [26]. A strong band observed around 1398 cm^{-1} can be assignable to $\nu_{C=S}$ vibration mode. In the metal complexes, the band corresponding to $\nu_{C=O}$ of succinimide ring was shifted to lower frequency range suggesting the coordination of carbonyl group with the metal ion. There is no shifting of bands at 1398 cm^{-1} indicating the absence of coordination of C=S group with the metal ion. The N-C-N stretching frequency of the Ligand at 1471 cm^{-1} was shifted towards lower values in all the complexes, indicating the involvement of the nitrogen of thiourea in coordination to the central metal ion.

TABLE 2: CHARACTERISTIC IR SPECTRAL DATA (cm^{-1}) OF SBT AND ITS METAL COMPLEXES

Compound	ν_{NH}	$\nu_{C=O}$	$\nu_{C=S}$	N-C-N	H_2O Coord	M-X	M-S
SBT	3285	1681	1398	1471	-	-	-
$MnCl_2.2H_2O.SBT$	3290	1673	1396	1463	3747,1590,808	423	-
$MnSO_4.2H_2O.SBT$	3320	1661	1395	1470	3774,1624,817	-	427
$CoCl_2.2H_2O.SBT$	3292	1677	1400	1466	3377,1591,808	425	-
$CoSO_4. 2H_2O.SBT$	3286	1670	1397	1464	3380,1632,811	-	424

^{1}H NMR Data of SBT: (DMSO/TMS, 500 MHz): The ^{1}H NMR spectra of SBT shows a singlet at δ 2.61 due to $–CH_2$ proton. A multiplet in the range δ 6.30-7.56 is assigned for aromatic protons. The singlet for one proton at δ 10.04 is assigned to– NH_2proton. Another singlet at δ 11.05 is assigned to -NH proton.

^{13}C NMR Data of SBT: (DMSO/TMS, 125 MHz): The number of signals of sharp peaks represents the number of carbons of the Ligand which are not chemically equivalent.^{13}C NMR - δ 173.6, 152.1, 148.3, 134.5, 126.4, 120.1, 110.1, 107.2, 55.3, 39.5, 28.6.

LC Mass Data of SBT: **Molecular formula:** $C_{13}H_{15}N_3O_3S$, Observed *m/z*=263.3, Calculated *m/z*=262.08.

Antimicrobial Activity: The microorganisms absorb metal ions in their cell walls, and as a result of respiration, processes of cells are disturbed, and protein synthesis is blocked, which is the requirement for further growth of organisms. The growth inhibition effects of metal ions are considerable. The only passage of lipid-soluble material is favored by the lipid membrane that surrounds the cell in accordance with the overtone's concept of cell permeability, as the antifungal activity is controlled by the lipophilicity factor. The overlap of ligand orbitals and the behaviour of metal ions to share charge with donor groups is reduced upon chelation and lipophilicity of complexes is enhanced. The proliferation of microorganisms is further restricted because the penetration of complexes in lipid membranes is facilitated by increased lipophilicity [27]. The impermeability of microbial cells and differences in ribosomes of cells are the major reason for variations in the effectiveness of different compounds against a variety of organisms. In most of the cases, ligands are less effective antimicobial agents than their metal complexes.

The *in-vitro* antibacterial activity of the synthesized ligand SBT and its metal complexes were evaluated against pathogenic bacteria *E. coli* (Gram-negative) and *S. aureus* (Gram-positive) by disc diffusion method.

Muller Hinton agar media was used for antibacterial activity to subculture various strains of microorganisms. 24 h grown culture was used as an inoculum on nutrient agar media. Disc diffusion method was performed to ascertain the antibacterial activity of the isolated ligand and its metal complexes in triplicates.

Zone of inhibition was measured for all the discs, and the average value of the mean was recorded for comparative analysis of antibacterial activity against Streptomycin and Penicillin as standard **Table 3**. Metal complexes exhibit good antibacterial activity against both the bacteria **Fig. 6**.

TABLE 3: ANTIBACTERIAL ACTIVITY OF SBT AND ITS METAL COMPLEXES

Compound	Antibacterial Activity	
	Zone of Inhibition (mm)	
	E. coli (250µg/disc)	*S. aureus* (250µg/disc)
SBT	9	8
$MnCl_2.2H_2O.SBT$	11	10
$MnSO_4.2H_2O.SBT$	15	14
$CoCl_2.2H_2O.SBT$	13	12
$CoSO_4.2H_2O.SBT$	14	10
Penicillin	-	22
Streptomycin	25	27

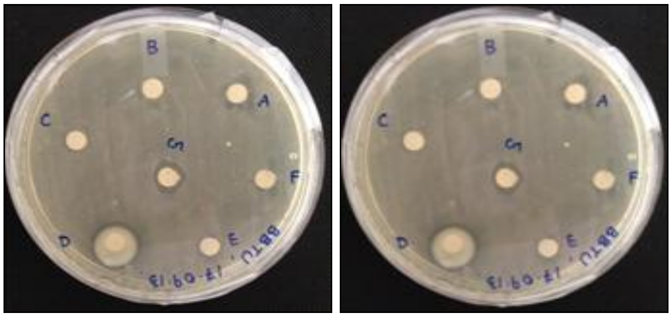

FIG. 6: ANTIBACTERIAL ACTIVITY OF SBT AND ITS METAL COMPLEXES

Antifungal Activity: To know the effect of ligand and the metal complexes against fungus, *Candida albicans* and *Aspergillus niger* were taken for analysis. Primarily, the activity was analyzed using a well-diffusion method with the concentrations of 100 and 400 µg/ml. after 24 h of incubation, the zone of clearance was observed. The antifungal activity of each compound was compared with the standard drug Flucanozole and is shown in **Table 4**.

Metal complexes are invariably found to be more toxic to the fungal species than the free ligand. The increased activity of the metal complexes against fungal species screened can be explained on the basis of chelation theory [28]. Chelation reduces the polarity of the metal ion considerably mainly because of partial sharing of its positive charge with donor groups and possible decolorization of π electron over the entire chelate ring. This aspect increases the lipophilic character of the neutral chelate favoring its diffusion through the lipid layers of the fungal membranes. Further, the presence of uncoordinated hetero atoms such as O, N, and S in the chelate molecule will involve forming hydrogen bonds with the active centers of cell membranes resulting in the interference of normal cell processes. Thus, the presence of polar groups like C=O, C=S *etc*. In the chelate molecules are expected to enhance their fungi toxicity [29-30]. The molecules tested have a greater chance of interaction with the nucleotide bases present in the cells of fungal species. Further, coordinatively unsaturated metal ions present in the metal complexes could achieve a higher coordination number by interacting with some of the enzymatic functional groups. This leads to increased uptake of the complex by the fungal species resulting in a high degree of growth inhibition **Fig. 7**.

TABLE 4: ANTIFUNGAL ACTIVITY OF SBT AND ITS METAL COMPLEXES

Compound	Antifungal Activity	
	A. niger (250µg/l)	*C. albicans* (250µg/l)
SBT	16	17
$MnCl_2.2H_2O.SBT$	18	19
$MnSO_4.2H_2O.SBT$	20	18
$CoCl_2.2H_2O.SBT$	17	19
$CoSO_4.2H_2O.SBT$	14	10
Flucanozole	21	22

FIG. 7: ANTIFUNGAL ACTIVITY OF SBT AND ITS METAL COMPLEXES

CONCLUSION: In conclusion, we have reported a simple method for the synthesis of Mannich base by one-pot three-component reactions. The metal complexes of Mn(II) and Co(II) complexes have been synthesized using the ligand and characterized on the basis of analytical, magnetic, and spectral data. The Mannich base coordinates through its thiourea nitrogen and oxygen of succinimide to the metal ion and acts as a neutral bidentate ligand. The complexes exhibit octahedral geometry. The ligand and its metal complexes were screened for antibacterial and antifungal activity. All the microbial studies showed that the metal complexes were more active.

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