Synthesis, Characterization & Anti-Bacterial Studies of Mannich base N-(phenyl(thioureido methyl) benzamide and its Metal Complexes

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Abstract - A novel Mannich base of N-(phenyl(thioureido methyl)benzamide (BBTU) and its coordination complexes with transition metals Mn,Co,Ni,Cu & Zn have been synthesized and characterized on the basis of elemental analysis, molar conductance, magnetic susceptibility measurements, UV-visible, IR , NMR & Mass spectral studies. The ligand (BBTU) and metal complexes were tested for antimicrobial properties.

Keywords: Mannich base, transition metal complexes, antimicrobial properties.

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1 Introduction

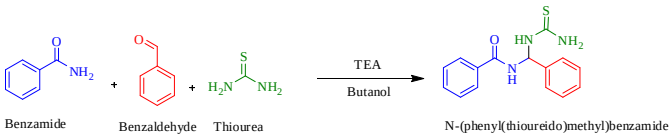
The major classes of pharmaceutical agents containing metal compounds are in current clinical use [1,2] and new areas of application of these metallic compounds are rapidly emerging. Monographs and major reviews also strongly support the growing importance of this discipline [3]. Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated with ligands. (Cox ,2005)[4]. Research works have shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. The advances in inorganic chemistry provide better opportunities to use metal complexes as therapeutic agents. But the mode of action of metal complexes on living organism is differing from non-metals. SophusJorgensen[5] in Denmark synthesized metal conjugates for the first time in the mid 1870's. In 1893 the major breakthrough in this field was occurred when Alfred Werner[6] investigated a series of compounds, which contained cobalt, chlorine and ammonia. The presence of nitrogen and sulfur atoms in the ligand provide more than one donor atoms, for complexation with metal ions[7]. The present work focuses the attention on the synthesis of one of these compound, it is N-(phenyl(thioureidomethyl)benzamide (BBTU) and some of its metal complexes with Mn(II),Co(II),Ni(II),Cu(II) & Zn(II).

2. Experimental methods:

2.1. Synthesis of the ligand BBTU:

To a solution of Benzamide (0.361g, 1 equiv.) in Butanol (3 mL), Aromatic aldehyde (0.48g, 1 equiv.) and Thiourea (0.93g, 1 equiv.) were added sequentially with small amount of TEA. The mixture was stirred at ambient temperature and progress of the reaction was monitored by TLC. After 6 days the crude material was formed and the solvent was evaporated in vacuum. The product was chromatographed over silica gel column using gradient elution of hexane ethyl acetate as solvent to afford BBTU **1a** as a white powder (scheme 1).

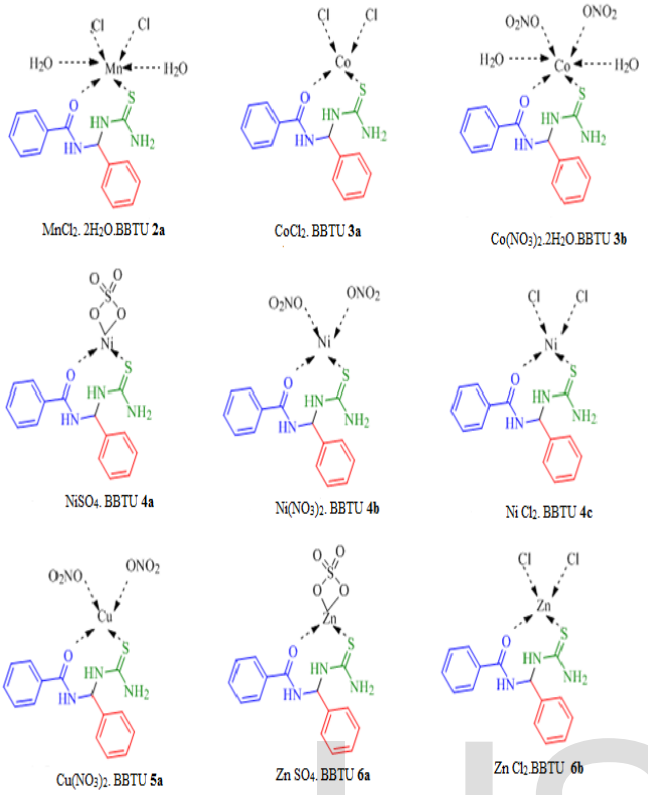
Scheme 1:



2.2. Synthesis of metal complexes of BBTU:

A solution of metal salts in water (5ml) was added slowly to the solution of ligand (0.002mM) in ethanol (10ml) with stirring at room temperature. The pH of the reaction mixture was adjusted to the range of 6.0 to 7.0 by addition of 0.1 M aqueous KOH solution. After the addition of base, the solid complex was formed after 2 days, and then it was filtered, washed with hexane, and dried in air. The tentative structures proposed for the metal complexes are shown in figure 1.

Figure 1: The structures of the metal complexes



3. Results and Discussions:

Spectral studies for BBTU

IR Data: Asymmetric ν_{NH} stretching frequency 3370cm^{-1}, Symmetric ν_{NH} stretching frequency 3171 cm^{-1}, δ_{NH} bending vibration 1379 cm^{-1}, Imide $\nu_{C=O}$ stretching frequency 1629 cm^{-1}, $\nu_{C=S}$ stretching frequency 782 cm^{-1}, Aromatic bending vibration 692 cm^{-1}.

^{1}H NMR Data (DMSO/TMS, 500.3MHz): δ2.57 (s, 4H), 6.61 (bs, 2H), 7.60 (d, 1H, *J*=1.00 Hz), 7.72 (s, 1H), 7.99 (dd,1H, *J*=8.00Hz), 8.24 (s, 1H), 8.34 (dd,1H, *J*=8.00Hz), 10.62 (s, 1H), 10.88 (s, 1H), ppm.

^{13}C NMR Data (DMSO/TMS, 125.7 MHz): δ179.4, 156.4, 147.8, 133.9, 129.6, 124.3, 40.0, 29.5 ppm.

LC Mass Data: Calculated for BBTU $C_{15}H_{15}N_3OS$ *m*/z=285.36; Found 286.65 (M+1).

4. Elemental analysis:

The physical properties and elemental analysis data of the ligand BBTU and its metal complexes are tabulated in table 1.

Colour and Percentage yield:

Compound	Colour	Yield %
BBTU **1a** ($C_{15}H_{15}N_3OS$)	White	98
$MnCl_2$. $2H_2O$.BBTU **2a** ($MnC_{15}H_{19}Cl_2N_3O_3S$)	White	85
$CoCl_2$. BBTU **3a** ($CoC_{15}H_{15}Cl_2N_5O_9S$)	Blue	92
$Co(NO_3)_2$.$2H_2O$.BBTU **3b** ($CoC_{15}H_{19}N_5O_9S$)	Grey	88
$NiSO_4$. BBTU **4a** (Ni $C_{16}H_{17}N_3O_5S_2$)	Green	95
$Ni(NO_3)_2$. BBTU **4b** ($NiC_{15}H_{15}N_5O_7S$)	Light Green	90
Ni Cl_2. BBTU **4c** ($NiC_{15}H_{15}Cl_2N_3OS$)	Green	82
$Cu(NO_3)_2$. BBTU **5a** (Cu $C_{15}H_{15}N_5O_7S$)	Dark Brown	90
Zn SO_4. BBTU **6a** ($ZnC_{16}H_{17}N_3O_5S_2$)	White	95
Zn Cl_2.BBTU **6b** ($ZnC_{15}H_{15}Cl_2N_3OS$)	Dull White	90

Table 1: Physical properties and elemental analysis data of the ligand BBTU and its metal complexes.

Compound	Found (Calculated %)					
	C	H	N	O	S	M
BBTU **1a** ($C_{15}H_{15}N_3OS$)	62.15 (63.13)	5.4 (5.2)	14.4 (14.7)	5.4 (5.60)	10.9 (11.2)	-
$MnCl_2$. $2H_2O$.BBTU **2a** ($MnC_{15}H_{19}Cl_2N_3O_3S$)	39.13 (40.28)	4.03 (4.28)	8.97 (9.40)	10.16 (10.73)	6.98 (7,18)	11.94 (12.28)
$CoCl_2$. BBTU **3a** ($CoC_{15}H_{15}Cl_2N_5O_9S$)	44.42 (43.39)	3.70 (3.64)	12 (10.12)	4.9 (3.85)	8.32 (7.73)	13.98 (14.19)
$Co(NO_3)_2.2H_2O$ .BBTU **3b** ($CoC_{15}H_{19}N_5O_9S$)	34.65 (35.72)	3.72 (3.80)	12.90 (13.89)	27.52 (28.55)	6.34 (6.36)	10.98 (11.69)
$NiSO_4$. BBTU **4a**($NiC_{16}H_{17}N_3O_5S_2$)	41.85 (42.31)	3..67 (3.77)	9.12 (9.25)	15.42 (17.61)	13.86 (14.12)	11.80 (12.92)
$Ni(NO_3)_2$. BBTU **4b** ($NiC_{15}H_{15}N_5O_7S$)	38.72 (38.49)	2.95 (3.23)	13.85 (14.96)	22.91 (23.93)	5.95 (6.85)	11.83 (12.54)
Ni Cl_2. BBTU **4c** ($NiC_{15}H_{15}Cl_2N_3OS$)	42.25 (43.42)	3.44 (3.64)	9.98 (10.13)	2.56 (3.86)	6.83 (7.72)	13.9 (14.14)
$Cu(NO_3)_2$. BBTU **5a** ($CuC_{15}H_{15}N_5O_7S$)	37.29 (38.10)	3.15 (3.20)	14.62 (14.81)	22.75 (23.68)	5,92 (6.78)	13.21 (13.44)
Zn SO_4. BBTU **6a**($ZnC_{16}H_{17}N_3O_5S_2$)	40.91 (41.7)	3.17 (3.72)	8.75 (9.12)	16.80 (17.36)	12.94 (13.92)	13.22 (14.19)
$ZnCl_2$.BBTU **6b** ($ZnC_{15}H_{15}Cl_2N_3OS$)	41.51 (42.72)	3.25 (3.59)	9.82 (9.96)	3.44 (3.79)	7.3 (7.59)	14.89 (15.50)

5. UV-Vis Spectroscopic studies:

The electronic spectra of the metal complexes were recorded for their ethanol solutions in the range of 190-800 nm. The blue cobalt complex is offered in a divalent state with symmetrical tetrahedral geometry. This hypothesis is supported by the number of maxima observed in the UV-Vis spectra[8] of the complex. The four maxima bands have been assigned to the transitions $^4A_2 \rightarrow {}^4T_2$, $^4A_2 \rightarrow {}^4T_1$,$^4A_2 \rightarrow {}^4T_1$ and CT. The magnetic moment is found to be 3.89 B.M at room temperature. The value of magnetic moment is suggested tetrahedral geometry for this complex.

The nitratoCo(II) complex exhibits four bands, which have been assigned to the transitions $^4T_{1g} \rightarrow {}^4T_{2g}$, $^4T_{1g} \rightarrow {}^4A_{2g}$, $^4A_{1g} \rightarrow {}^4T_{1g}$ and CT. The calculated magnetic moment value is 4.80 B.M. This value is in agreement with the values expected for an octahedral geometry.

The nitratoCu(II) complex exhibits four bands which have been assigned to the transitions $^2B_{1g} \rightarrow {}^2A_{1g}$,$^2B_{1g} \rightarrow {}^2B_{2g}$, $^2E_g \rightarrow {}^2T_{2g}$ and CT. The calculated magnetic moment value is 4.80 B.M. This is in agreement with the values expected for pseudo tetrahedral geometry [9-11].

The sulphate of Ni(II) complex exhibits four bands, which have been assigned to the transitions $^1A_{1g} \rightarrow {}^1A_{2g}$,$^1A_{1g} \rightarrow {}^1B_{1g}$,$^1A_{1g} \rightarrow {}^1E_g$ and CT. The calculated magnetic moment value is 2.10 B.M. This is in agreement with the values expected for square planar geometry.

The nitrato and chloro complexes of Ni(II)exhibit five bands, which have been assigned to the transitions $^3T_{1g} \rightarrow {}^3T_{2g}$,$^3T_{1g} \rightarrow {}^3A_{2g}$,$^3T_{1g} \rightarrow {}^3T_{2g}$ and CT. The calculated magnetic moment value is 3.52 B.M. This is in agreement with the values expected for tetrahedral geometry[12].

The chloro complex of Mn(II) exhibits three bands, which have been assigned to the transitions $^6A_{1g} \rightarrow {}^4T_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}$ and CT. The calculated magnetic moment value is 2.46 B.M. This complex is assigned to octahedral geometry [13].

The Zn complexes do not display electronic transitions and they are diamagnetic in nature. However on the basis of 1:1 stoichiometry, molar conductance and IR spectral data, these metal complexes are tentatively assigned for the usual 4-coordinated tetrahedral geometry.

Molar conductance, magnetic moment, assigned transitions with λ_{max} and geometry of the ligand and its metal complexes are tabulated in table 2.

Table 2: Molar Conductance (in DMF), magnetic moment, assigned transitions with λ_{max} and geometry of the metal complexes.

Name of the Complex	Λm (ohm^{-1} cm^2 mol^{-1})	μ_{eff} (B.M)	λ_{max} (cm^{-1})	Transition Assignment	Geometry
$MnCl_2.2H_2O$ BBTU**2a**	72	4.99	18362 22457 31293	$^6A_{1g}\rightarrow{}^4T_{1g}$ $^6A_{1g}\rightarrow{}^4T_{2g}$ CT	Octahedral
$CoCl_2$.BBTU**3a**	64	3.89	3909 6748 15117 27473	$^4A_2\rightarrow{}^4T_2$ $^4A_2\rightarrow{}^4T_1$ $^4A_2\rightarrow{}^4T_1$ CT	Tetrahedral
$Co(NO_3)_2.2H_2O$.BBTU**3b**	57.5	5.28	6713 14265 18842 29086	$^4T_{1g}\rightarrow{}^4T_{2g}$ $^4T_{1g}\rightarrow{}^4A_{2g}$ $^4A_{1g}\rightarrow{}^4T_{1g}$ CT	Octahedral
$NiSO_4$ BBTU**4a**	45	1.48	12593 20463 27868 35714	$^1A_{1g}\rightarrow{}^1A_{2g}$ $^1A_{1g}\rightarrow{}^1B_{1g}$ $^1A_{1g}\rightarrow{}^1E_g$ CT	Square planar
$Ni(NO_3)_2$.BBTU**4b**	66	3.56	3935 8718 15016 24039, 34483	$^3T_{1g}(F)\rightarrow{}^3T_{2g}$ $^3T_{1g}(F)\rightarrow{}^3A_{2g}$ $^3T_{1g}(F)\rightarrow{}^3T_{2g}$ CT	Tetrahedral
$NiCl_2$.BBTU**4c**	96	4.30	3865 8395 13734 25037, 31420	$^3T_{1g}\rightarrow{}^3T_{2g}$ $^3T_{1g}\rightarrow{}^3A_{2g}$ $^3T_{1g}\rightarrow{}^3T_{2g}$ CT	Tetrahedral
$Cu(NO_3)_2$.BBTU**5a**	93	2.79	9275 10374 12557 24330, 28327	$^2B_{1g}\rightarrow{}^2A_{1g}$ $^2B_{1g}\rightarrow{}^2B_{2g}$ $^2E_g\rightarrow{}^2T_{2g}$ CT	Pseudo-Tetrahedral

6. IR Spectra:

The broad band that appeared in the IR spectrum[14] of the Mannich base BBTU at 3370 cm^{-1} is assigned to asymmetric NH stretching vibration of secondary amino group and the band that appeared at 3171cm^{-1} is for symmetric NH vibration. In addition, a band at 1379 cm^{-1} is assigned for δ_{NH}. The band appearing at 1629cm^{-1} confirms the presence of imide carbonyl group. The evidence for CNC stretching vibration is observed at 1121cm^{-1} a C-S stretching vibration of thiourea is appeared at 782cm^{-1}. Aromatic bending vibrations are confirmed at 692cm^{-1}. For all the metal complexes, the NH stretching vibrations (symmetric & asymmetric) are observed at the range of 3170-3380 cm^{-1}. Moreover all the metal complexes also show bands in the range of 710-790 cm^{-1} which confirms M-S linkage. The observation of a band in the spectra of the metal complexes in the range 600-650cm^{-1} is assigned to M-O stretching vibrations. However, the weak absorptions in the range 450-490 cm^{-1} for chloro complexes were assigned to M-C linkage[15].

Table 3:

Characteristic IR Absorption Frequencies (cm^{-1}) of BBTU and its Metal Complexes.

Compound	ν_{NH}	ν_{CO}	ν_{CNC}	ν_{M-O}	ν_{M-X}
BBTU **1a**	3375,3174	1626	1194	-	-
$CoCl_2$. .BBTU **3a**	3380,3180	1646	1118	630	480
$Co(NO_3)_2.2H_2O$ .BBTU **3b**	3367,3170	1644	1121	633	-
$Cu(NO_3)_2$. .BBTU **5a**	3366,3161	1659	1160	645	-
$NiSO_4$. BBTU **4a**	3327,3150	1633	1103	636	-
$Ni(NO_3)_2$. BBTU **4b**	3359,3177	1658	1143	635	-
Ni Cl_2. BBTU **4c**	3375,3180	1691	1121	691	482
Zn SO_4. BBTU **6a**	3344,3165	1627	1111	632	-
Zn Cl_2. BBTU **6b**	3355,3182	1624	1123	689	475
$MnCl_2.2H_2O$ .BBTU **2a**	3357, 3189	1650,	1105	622	490

7. Antibacterial activity:

The ligand showed effective antibacterial activity against

Escherichia coli (Gram negative), Bacillus sp.(Gram positive) and Staphylococcus aureus(Gram positive). 24 hours grown culture was used as an inoculum on nutrient agar media. Disc diffusion method was performed to ascertain antibacterial activity[16] of the isolated compound 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 the comparative analysis of antibacterial activity against Streptomycin as standard. Zone of inhibition diameter of 14 mm against *Bacillus sp.* and a diameter of 18 mm against *S.aureus* was observed at a concentration of 50 µg/µL of basic compound. No inhibition was observed in *E.coli* plates inferring that the compound specifically targets Gram Positive bacteria. But the metal complexes of the ligand showed inhibition action against both gram positive as well as gram negative bacteria involved in the study. The $ZnSO_4$ metal complex showed maximum zone of inhibition of 22 mm against *S.aureus*. The reason for this is the breakdown of cell wall components of the bacteria. Table 4. represents the zone of inhibition of various metal complexes at a concentration of 50µg/µL each. This study evidences the antibacterial activity of the ligand and its metal complexes.

Table 4: Antibacterial activity of the metal comlexs

S. No.	Metal complexes	Concentration	Zone of Inhibition (mm)		
			E.coli	*S.aureus*	*Bacillus sp.*
1.	BBTU	50µg/µL	8	11	7
1.	$CoCl_2$ .BBTU	50µg/µL	10	13	8
2.	$Cu(NO_3)_2$.BBTU	50µg/µL	0	9	10
3.	$CuSO_4$.BBTU	50µg/µL	11	16	15
4.	$NiSO_4$.BBTU	50µg/µL	9	12	11
5.	$NiCl_2$.BBTU	50µg/µL	10	12	10
6.	$ZnCl_2$.BBTU	50µg/µL	12	14	15
7.	$ZnSO_4$.BBTU	50µg/µL	16	22	12
8.	Streptomycin	20µg/µL	30	32	24

8. Conclusion:

The new mannich base (N-(phenyl(thioureido methyl)benzamide) and Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) metal chelates of the mannich base (N-(phenyl(thioureido methyl)benzamide) were synthesized and characterized by various chemical and spectral analysis. Based on the spectral data the ligand was found to coordinate through carbonyl oxygen of benzamide and sulphur atom of thiourea. The synthesized ligand and their metal complexes showed anti bacterial activities.

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