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Full Paper

Cobalt (II), nickel (II), copper (II) and zinc (II) complexes of 1-(phenyl(phenylamino) methyl)pyrrolidine-2,5-dione and 2-((phenylamino)methyl) isoindoline-1,3-dione and their biological activity

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ABSTRACT: *The new Mannich bases 1-(phenyl(phenylamino)methyl)pyrrolidine-2,5-dione (SBA) was synthesized from the condensation of succinimide, benzaldehyde and aniline. 2-((phenylamino)methyl)isoindoline-1,3-dione (PFA) was derived from pthalimide, formaldehyde and aniline. The general formula of the Co(II), Ni(II), Cu(II) and Zn(II) chloro complexes,* ML_2X_2 *are reported. The ligands and the complexes have been characterized by various physical-chemical techniques such as elemental analysis, molar conductance, magnetic susceptibility measurements, infrared and electronic spectra. The spectral analysis to ascertain mode of bonding and overall geometry of the complexes revealed octahedral geometries.*

Keywords*: Mannich bases; metal complexes; octahedral geometries*

Introduction

The synthesis, characterization and spectral study of metal complexes containing biologically important ligands assume importance because certain metal ions are active in many biological processes [1-3]. The fact that transition metals are essential metallic elements and exhibit great biological activity when associated with certain metal–protein complexes, participating in oxygen transport, electronic transfer reactions or the storage of ions [4], has created attention in the study of systems containing these metals. There

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has been considerable interest directed towards the isolation of new complexes of these ligands and their spectral and magnetic characterization [5, 6]. Mannich type reactions are among the most important carbon-carbon bond forming reactions in organic synthesis [7]. They provide amino methylated/benzylated compounds which are important synthetic intermediates for various pharmaceuticals and natural products [8]. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen containing compounds in drugs and natural products [9]. Metal complexes of succinimide and phthalimide are of interest due to their unique structural features and potential pharmacological applications [10-11]. In view of these findings, Mannich bases of succinimide and phthalimide and their metal complexes have been synthesized, characterized and screened them for their biological activity.

Material and Methods

The chemicals used in the synthesis were obtained from Aldrich Chemical Company and were used without further purification. The solvents used were of spectroscopic grade. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on a Bruker Advance DPX 300 MHz Ultra-Shield FTNMR Spectrophotometer in DMSO-d_6 and $CDCl_3$ with TMS as internal reference. Chemical shifts are expressed in δ units (ppm). Ultraviolet-visible (UV-Vis) absorption spectra were recorded on Perkin-Elmer Spectrophotometer (EZ 301) at the wavelength of maximum absorption (λ_{max}) in dimethylsulfoxide (DMSO)/*N,N*-dimethylformamide (DMF). All melting points were taken in open capillary tubes in ^{o}C by using Elico instrument and mass spectra on a LUNA instrument. The micro-elemental results were obtained on a Vario-EL instrument. The human pathogenic bacterial species (*Pseudomonas aeuroginosa, Escherichia coli, Salmonella typhi, bacillus cereus, and klebsilla pneumonia*) were used for the anti microbial studies.

Microbial inoculums preparation

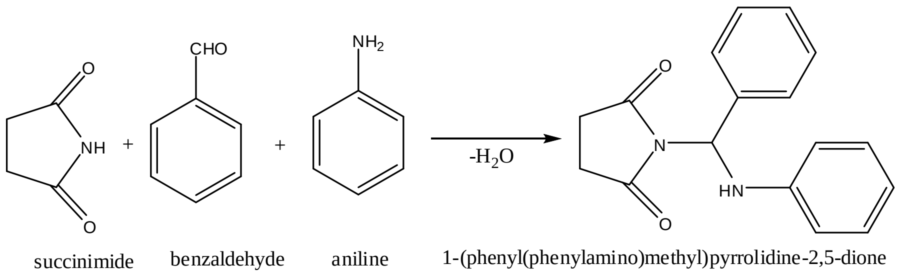
The young microbial inoculums/culture was prepared and used in the entire research period. The nutrient broth (NB) for bacteria and potato dextrose broth (PDB) for fungi were prepared and poured into tubes and sterilized. The pure microbial cultures collected were inoculated in the tubes using inoculation needles and loops. Then these tubes were incubated at different temperatures and time duration (at 37 °C and 24-48 hours for bacteria and at 27 °C and 48-72 hours for fungi). 20 mg of synthesized organic compounds dissolved in 2 mL of DMSO were used as a stock solution. From the stock solution, various concentrated discs (60 µg) were prepared.

Synthesis

Synthesis of 1-(phenyl(phenylamino)methyl)pyrrolidine-2,5-dione (SBA)

Aniline (10 mL, 0.1M) was added slowly to a solution of succinimide (9.09 g, 0.1M) in water, taken in a beaker. Benzaldehyde (10 mL, 0.1M) was added in drops with stirring of the solution. The mixture first become oily and then after 10 days it slowly turned into a white crystalline mass which was separated by suction filtration and washed several times with water. The product was dried at 60 °C and recrystallized using toluene by slow evaporation method.

Molecular formula: $C_{17}H_{16}N_2O_2$, Yield: 76%, MP: 73-74 °C, Mol. wt: 280.32. FT- IR KBr in cm^{-1}: 3440, 3333 (NH), 3111, 3059 (CH aromatic), 1691, 1625 (C=O), 1182 (C-N-C), 785, 747 (mono substituted benzenoid ring). ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 4H), 8.20 (s, NH), 6.14 (d, 2H), 6.52-6.58 (m, 5H phenyl ring), 7.51-7.27 (m, 5H aniline). ^{13}C NMR (300 MHz, $CDCl_3$) δ 29.57 (s, 2C, $(CH_2)_2$), 64.18 (s, 1C, CH), 108.53 (s, C), 114.46-160.48 (m, 5C, benzyl ring), 177.71 (s, 2C, C=O). FABMS m/z: 280.32 ($C_{17}H_{16}N_2O_2$), base peak m/z 182.24 ($C_{13}H_{12}N^{+\cdot}$); 203.21 ($C_{11}H_{11}N_2O_2^{+\cdot}$); 104.98 ($C_7H_7N^{+\cdot}$); 77.10 ($C_6H_5^{+\cdot}$). Calculated: C 72.84 %, H 5.75 %, and N 9.99 %, O 11.42%. Found: C 72.89 %, H 5.71 %, and N 9.96 %, O 11.44 %.



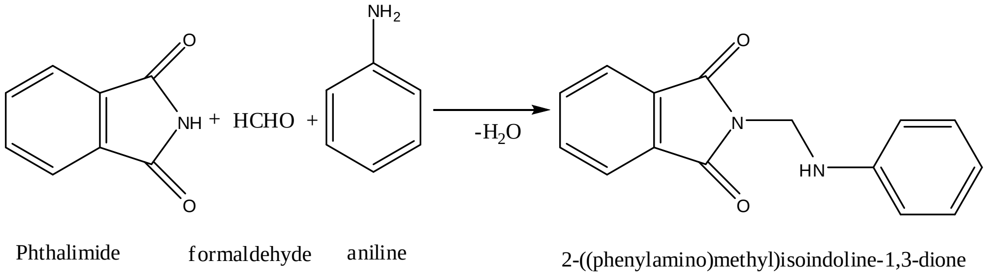
Scheme1

Synthesis of 2-((phenylamino)methyl)isoindoline-1,3-dione (PFA)

9.5 g (0.1mol) of phthalimide and 10 mL (0.1mol) of formaldehyde were dissolved in minimum amount of ethanol and the contents were mixed well at room temperature until a clear solution was obtained. 10 mL (0.1mol) of aniline was added to this mixture. After 10 days a yellow solid was obtained and it was washed with ethanol several times and dried in the air oven at 60 °C and recrystallized from ethanol.

Molecular formula: $C_{15}H_{12}N_2O_2$, Yield: 87, MP: 132-133 °C, Mol. wt: 252.26. FT IR KBr in cm^{-1}: 3447, 3384 (-NH), 3050, 2957 (CH aromatic), 1765, 1708 (C=O stretching), 1602 (C=C, C=N stretching), 1510 (NH bending), 1407 (C-N stretching), 1166 (C-N-C stretching), 722 (benzene CH out of plane bending). ^1H NMR (300 MHZ, $CDCl_3$) δ 2.47 (s, 4H), 3.32 (s, NH), 4.75 (d, 2H), 6.76-7.09 (m, 5H, phenyl ring). ^{13}C NMR (300 MHZ, $CDCl_3$) δ 28.21 (s, 2C, $(CH_2)_2$), 48.46 (s, 1C, CH_2), 108.53 (s, C), 113.57-144.57 (m, 5C, phenyl ring), 177.49 (s, 2C, C=O). FABMS m/z: 252.27 ($C_{15}H_{12}N_2O_2^{\cdot +}$); m/z: ($C_9H_7N_2O_2^{\cdot +}$); m/z: 160.14 ($C_9H_6NO_2^{\cdot +}$); m/z: 77.10 ($C_6H_5^{\cdot +}$). Calculated: C 71.51 %, H

4.79 %, and N 11.10 %, O 12.68 %. Found: C 71.39 %, H 4.63%, N 11.21%, O 12.77 %.



Scheme 2

Synthesis of metal complexes

Ethanolic solution of Mannich base (0.1M) was mixed with hot ethanolic solution of metal (II) chloride (0.05M) and digested on a water bath for 50 minutes. The content was concentrated and cooled. The solid product obtained was filtered, washed with ethanol and dried under vacuum.

Results and Discussion

Physical characteristics, micro analytical and magnetic susceptibility data of the complexes are given in Table 1. The analytical data of all the complexes correspond to the general formula ML_2X_2. Magnetic susceptibility values of the complexes at room temperature are consistent with octahedral geometry around the central metal ions. The chelates show no appreciable conductance, and this supports the hypothesis of their neutral nature. The electronic absorption spectra of the Mannich bases and their Co (II), Ni (II), Cu (II) and Zn (II) complexes were recorded at room temperature using DMSO as solvent. The electronic spectra of Co(II) complex showed two spin-allowed transitions at 17,876 and 21,714 cm^{-1} assignable to $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$ and $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ transitions respectively, are in conformity with octahedral arrangements for Co(II) ion [13]. The appearance of a band at 19,244 cm^{-1} due to $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$ transition favors an octahedral geometry [14] for the Ni(II) complex. The absence of any band below 10,000 cm^{-1} eliminates the possibility of a tetrahedral environment in this complex. Only one broad band is observed at 16,638 cm^{-1} in the electronic spectrum of the Cu(II) complex assigned to $^2E_g \rightarrow {}^2T_{2g}$ transition similar to octahedral [12] arrangement which is supported by its magnetic moment value (1.8 μB). Though three transitions are expected in this case, they are very close in energy and often appear in the form of one broad band envelope. No transitions were observed in the visible region for the Zn (II) complex consistent with the d^{10} configuration of the Zn^{2+} ion. This complex is also found to be diamagnetic as expected for the d^{10} configuration. The suggested structure for the complexes is shown in Figure 1.

Table 1. Physical characterization, analytical, molar conductance and magnetic susceptibility data of the ligand and its complexes.

Compound	***Color***	***Contents (found/calcd) %***					***$\wedge_m$ Ohm^{-1} cm^2 mol^{-1}***	***μ_{eff}, μ_B***
		Metal	**C**	**H**	**N**	**O**		
Ligand-SBA	Brown	-	58.56/58.55	5.42/5.49	20.47/20.45	15.55/15.52	---	---
SBA -$CoCl_2$	Dark brown	10.91	44.46/44.45	4.10/4.10	15.56/15.53	11.85/11.87	11.1	4.77
SBA -$NiCl_2$	Light green	10.87	44.48/44.44	4.11/4.12	15.56/15.55	11.85/11.88	11.3	3.81
SBA- $CuCl_2$	Dark green	11.66	44.09/44.01	4.07/4.10	15.42/15.40	11.75/11.76	12.6	1.89
SBA-$ZnCl_2$	Colorless	11.96	43.94/43.90	4.06/4.05	15.37/15.38	11.71/11.73	10.2	---
Ligand-PFA	Yellow	-	71.41/71.42	4.77/4.79	11.14/11.10	12.67/12.68		
PFA-$CoCl_2$	Brown	7.93	54.92/54.90	4.34/4.35	11.30/11.28	21.52/21.53	11.9	4.70
PFA-$NiCl_2$	Light green	7.90	54.94/54.95	4.34/4.33	11.31/11.33	21.52/21.55	12.0	3.66
PFA-$CuCl_2$	Dark green	8.49	54.58/54.55	4.31/4.30	11.23/11.21	21.38/21.36	12.1	1.80
PFA-$ZnCl_2$	Colorless	8.72	54.44/54.46	4.30/4.33	11.20/11.17	21.33/21.36	10.2	---

Table 2. Important IR Absorption Bands (cm^{-1}) of SBA, PFA and of Co (II), Ni (II), Cu (II) and Zn (II) Complexes.

Compound	***ν_{NH}***	***$\nu_{C=O}$***	***ν_{CNC}***	***ν_3***	***ν_4***	***ν_1***	***ν_2***	***ν_5***	***ν_6***
SBA	3333, 3230	1691	1182	-	-	-	-	-	-
SBA -$CoCl_2$	3300	1631	1098	1142, 1005, 984	788 631, 601	872	471	-	-
SBA -$NiCl_2$	3335	1631	1071	1170, 990	633, 604	828	543	-	-
SBA- $CuCl_2$	3313	1625	1100	1100, 1039, 996	778, 701	871	532	-	-
SBA-$ZnCl_2$	3390	1598	1087	-	-	1313	1018	1429	824
PFA	3447,3384	1765, 1708	1166	-	-	-	-	-	-
PFA-$CoCl_2$	3485	1635	1109	1151, 987	754, 612	852	490	-	-
PFA-$NiCl_2$	3548	1627	1101	-	-	1310	1052	1384	802
PFA-$CuCl_2$	3151	1622	1100	984	632	860	459	-	-
PFA-$ZnCl_2$	3335	1621	1100	1109	641	-	-	-	-

From the above spectral data the tentative assignment of the complexes are shown in figures 1 and 2.

Antimicrobial study

All the ligands and complexes were tested for *in vitro* antimicrobial activity. The antimicrobial activity values of the compounds against pathogenic gram-positive and gram-negative bacteria and fungi are presented in Tables 3 and 4. The compound SBA and PFA showed poor antibacterial activity, while Co (II) complexes showed good activity against *Pseudomonas aeuroginosa (PC), E. coli(EC), bacillus cereus, salmonella typhi, klebsilla pneumonia* bacteria. The antifungal activity of the compounds was studied with pathogenic fungi, and the results are given in Table 5. Ampotericin B is used as a reference. All the compounds showed significant antifungal activity, especially compound PFA-Co complex, which showed higher activity than others. It was found that most of the synthesized compounds possess antimicrobial properties. It is observed from these studies that metal chelates presented higher activity than the free ligand. Such increased activity of the metal chelates can be explained on the basis of Overtone's concept and chelation theory [15]. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid soluble materials due to which liposolubility is an important factor that controls antimicrobial activity. On chelation, the polarity of the metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of metal binding sites on the enzymes of the microorganism.

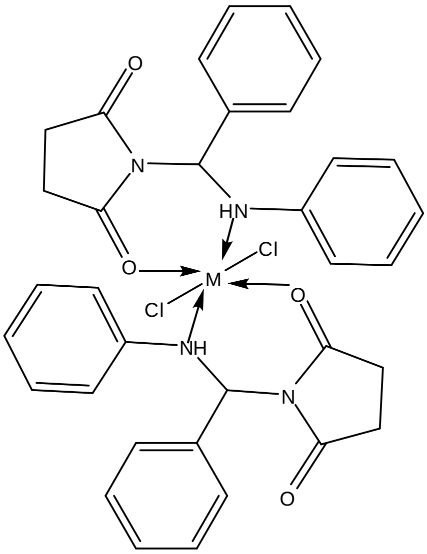


Figure 1. 1-(phenyl(phenylamino)methyl)pyrrolidine-2,5-dione metal complexes.

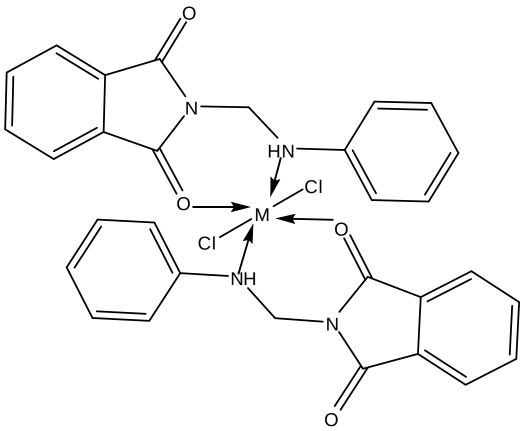


Figure 2. 2-((phenylamino)methyl)isoindoline-1,3-dione metal complexes.

Table 3. Antibacterial activity zone of inhibition in mm against Pseudomonas aeruginosa(PA), E-coli(EC), salmonella typhi (ST), klebsilla pneumonia(KP), bacillus cereus (BC).

Compounds	***ST***	***KP***	***EC***	***BC***	***PA***
Streptomycin	29	26	33	23	30
SBA	-	2	-	-	-
SBA-$CoCl_2$	12	-	4	-	18
SBA-NiCl2	16	4	-	-	-
SBA-$CuCl_2$	-	8	-	-	-
PFA	3	-	3	-	-
PFA-$CoCl_2$	22	13	15	16	-
PFA-$NiCl_2$	-	-	-	-	-
PFA-$CuCl_2$	12	8	-	12	20
DMSO	-	-	-	-	-

Table 4. Antibacterial study of investigated compounds (MIC × 10^{-2} mol/L).

Compounds	***MIC(μg/mL)***	***MBC(μg/mL)***
SBA	KP-1.56	---
SBA-$CoCl_2$	ST- 1.56	---
SBA-$CoCl_2$	EC-12.5	---
SBA-$CoCl_2$	PA- 3.125	6.25
SBA-$NiCl_2$	ST- 3.125	6.25
SBA-$NiCl_2$	KP -6.25	---
PFA	ST-1.5	---
PFA	EC-1.52	---
PFA-$CoCl_2$	ST- 1.56	---
PFA-$CoCl_2$	KP- 12.5	---
PFA-$CoCl_2$	EC-6.25	12.5
PFA-$CoCl_2$	BC-1.525	3.125
PFA-$CuCl_2$	ST – 4.25	---
PFA-$CuCl_2$	KP-5.5	---
PFA-$CuCl_2$	BC-1.5	---
PFA-$CuCl_2$	PA-3.12	---

Table 5. Antifungal activity zone of inhibition in mm.

Compounds	***A.O***	***A. F***
Ampotericin B	20	16
SBA	-	-
SBA -$CoCl_2$	3	-
SBA –$NiCl_2$	-	-
SBA -$CuCl_2$	4	6
PFA	12	-
PFA -$CoCl_2$	18	12
PFA -$NiCl_2$	-	-
PFA -$CuCl_2$	2	-
DMSO	-	-

PA- *Pseudomonas aeuroginosa,*
EC- *E-coli,*
BC- *bacillus cereus,*
ST – *salmonella typhi*
KP- *klebsilla pneumonia*
A.O - *Aspergillus oryzae*
A.F - *Aspergillus fumigates*
MIC- minimum inhibitory concentration

Two fold serial dilution method
50; 25; 12.5; 6.25; 3.125; 1.525; 0.7825; 0.3912.
----- No activity, No minimum bactericidal concentration (MBC)

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