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Synthesis, spectroscopic and thermal characterization of sulpiride complexes of iron, manganese, copper, cobalt, nickel, and zinc salts. Antibacterial and antifungal activity

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ABSTRACT

Sulpiride (SPR; L) is a substituted benzamide antipsychotic which is reported to be a selective antagonist of central dopamine receptors and claimed to have mood-elevating properties. The ligation behaviour of SPR drug is studied in order to give an idea about its potentiality towards some transition metals in vitro systems. Metal complexes of SPR have been synthesized by reaction with different metal chlorides. The metal complexes of SPR with the formula $[MCl_2(L)_2(H_2O)_2]\cdot nH_2O$ [M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II); n = 0–2] and $[FeCl_2(HL)(H_2O)_3]Cl\cdot H_2O$ have been synthesized and characterized using elemental analysis (CHN), electronic (infrared, solid reflectance and ^{1}H NMR spectra) and thermal analyses (TG and DTA). The molar conductance data reveal that the bivalent metal chelates are non-electrolytes while Fe(III) complex is 1:1 electrolyte. IR spectra show that SPR is coordinated to the metal ions in a neutral monodentate manner with the amide O. From the magnetic and solid reflectance spectra, octahedral geometry is suggested. The thermal decomposition processes of these complexes were discussed. The correlation coefficient, the activation energies, E^*, the pre-exponential factor, A, and the entropies, ΔS^*, enthalpies, ΔH^*, Gibbs free energies, ΔG^*, of the thermal decomposition reactions have been derived from thermogravimetric (TG) and differential thermogravimetric (DTG) curves. The synthesized ligand and its metal complexes were also screened for their antibacterial and antifungal activity against bacterial species (*Escherichia coli* and *Staphylococcus aureus)* and fungi (*Aspergillus flavus* and *Candida albicans*). The activity data show that the metal complexes are found to have antibacterial and antifungal activity than the parent drug and less than the standard.

1. Introduction

Sulpiride, 2-methoxy-N-((1-propylpyrrolidine-2-yl) methyl)-5-sulphamoyl-benzamide (Fig. 1 [1]), is a substituted benzamide antipsychotic which is reported to be a selective antagonist of central dopamine (D_2, D_3 and D_4) receptors. It is also claimed to have mood-elevating properties [2]. A literature survey also reveals several methods for assaying SPR, involving HPLC [3], TLC [4,5], fluorometric [6], spectrophotometric [7,8], flow injection chemiluminometric [9], capillary liquid chromatography [10], electrophoresis [11–16], oscillopolarographic [17] and adsorptive stripping voltammetric methods [18].

The synthesis and characterization of new metal complexes with antibacterial agents are of great importance for understanding the drug–metal ion interaction and for their potential pharmacological use. The objective of this study is the isolation and characterization of the Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) complexes using spectroscopic and thermal analyses techniques. The IR spectra are used to infer the mode of bonding of SPR with these essentially biological active elements. The thermal behaviour of these complexes is also studied. The antibacterial and antifungal activities of the investigated complexes were tested against *Escherichia coli* (Gram −ve), *Staphylococcus aureus* (Gram +ve) and *Aspergillus flavus* and *Candida albicans* (antifungal). Important findings are obtained.

2. Experimental

2.1. Materials and reagents

All chemicals used were of the analytical reagent grade (AR), and of highest purity available. They included SPR drug (Unipharma, Egypt); Cu(II) chloride dihydrate (Prolabo); Fe(III), Co(II) and Ni(II) chlorides hexahydrates (BDH); Zn(II) chloride dihydrate (Ubichem)

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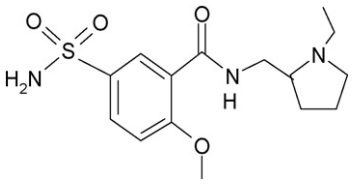

Fig. 1. Structure of sulpiride drug.

and Mn(II) chloride (Prolabo). Organic solvents used included absolute ethyl alcohol, diethylether, and dimethyl formamide (DMF). These solvents were spectroscopic pure from BDH. Hydrogen peroxide, hydrochloric and nitric acids (MERCK) were used. De-ionized water collected from all glass equipments was usually used in all preparations. The test organisms were kindly supplied from the microbiological resource center, Ain Shams University, Faculty of Agriculture, Egypt (CAIM, Cairo Mircen), and from Bacteriological Department of National Organization for Drug Control and Research (NODCAR), ATCC, American type culture collection. Bacterial test organisms were inoculated on nutrient agar slants for 24 h at 37 °C. Yeast and fungi organisms were inoculated on Sabouroud's dextrose agar slants and incubated at 28 °C for 48 h (Jacobs and Gerstein, 1960). Several workers used these organisms repeatedly as test organisms.

2.2. Instruments

The molar conductance of solid complexes in DMF was measured using Sybron-Branstead conductometer (Meter-PM.6, $E = 3406$). Elemental microanalyses of separated solid chelates for C, H, N and S were performed at the Microanalytical Center, Cairo University. The analyses were repeated twice to check the accuracy of the data. Infrared spectra were recorded on a Perkin-Elmer FT-IR type 1650 spectrophotometer in wave number region 4000–400 cm^{-1}. The spectra were recorded as KBr pellets. The ^1H NMR spectra were recorded using 300 MHz Varian–Oxford Mercury. The molar magnetic susceptibility was measured on powdered samples using the Faraday method. The diamagnetic correction was made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. The thermogravimetric (TG and DTG) and differential thermal (DTA) analyses were carried out in dynamic nitrogen atmosphere (20 ml min^{-1}) with a heating rate of 10 °C min^{-1} using Shimadzu TG-60H and DTA-60H thermal analyzers.

2.3. Synthesis of metal complexes

Ethanolic hot solution (60 °C) of appropriate metal chlorides (0.126, 0.237, 0.240, 0.237, 0.170 and 0.172 g of Mn(II), Ni(II), Fe(III), Co(II), Cu(II) and Zn(II), respectively, 1 mmol) in an ethanol–water mixture (1:1) was added to the hot solution (60 °C) of SPR drug (0.351 g, 2 mmol) in the same solvent (25 ml). The resulting mixture was stirred under reflux for 2 h whereupon the complexes precipitated. They were collected by filtration, washed several times with a 1:1 ethanol:water mixture and diethyl ether.

2.4. Biological activity

The antimicrobial activities were carried out by disc diffusion technique as described in British Pharmacopoeia (2000). Nutrient agar was melted at 45 °C and inoculated by the cell suspension (1 ml/100 ml) bacteria or yeast. The flask was shaken well and poured in to a Petri-dish (15 cm^{-2} in diameter). Filter paper discs (6 mm) Whatman No. 2 were thoroughly moistened by antibiotics (50 μg), the treated discs were aseptically transferred and placed upon the surface of the inoculated plates with tested organisms and kept in a refrigerator for 1 h to permit diffusion on antimicrobial substances. The plates were incubated at 37 °C for 24 h in case of bacteria and at 28 °C for 48 h in case of fungi. The zones of inhibition were measured in mm. The mean values of inhibitions were calculated from triple reading in each test [19,20].

The following media were used in studding the antimicrobial properties of drug complexes. The weights are given in gram per one-liter medium.

Nutrient agar medium (pH 7.4): It consists of beef extract (1 g), yeast extract (2 g), peptone (5 g), sodium chloride (5 g), agar agar (15 g) and distilled water (100 ml).

Sabouroud's dextrose agar medium (pH 5.6): It consists of peptone (10 g), dextrose (20 g), agar agar (15 g) and distilled water (100 ml).

3. Results and discussion

The formation of metal complexes with organic compounds has long been recognized. However, the binary complexes of the cited drug with metal ions have not been studied yet, although they may be an area of interest. This is because they may affect the bioavailability of these drugs as certain metal ions were present in relatively appreciable concentration in biological fluids [21].

3.1. Mass spectrum of the SPR drug

The electron impact mass spectrum of SPR ligand is recorded and the important peaks and their relative intensities for the molecular ions are shown in Scheme 1. Mass spectrum of the studied drug is characterized by moderate to high relative intensity molecular ion peaks at 70 eV. Scheme 1 shows a well-defined parent peak at $m/z = 98$ (R.I. = 100%) which may be due to $C_6H_{13}N$. The other molecular ion peaks appeared in the mass spectrum (abundance range from 1.0% to 100%) may be attributed to the fragmentation of SPR molecule obtained from the rupture of different bonds inside the molecule. The suggested mechanism of fragmentation can help in understanding the way of metabolism of the drug in the human body.

3.2. Elemental analyses of the complexes

The results of elemental analyses listed in Table 1 suggest that the complexes are formed in 1:2 [metal]:[SPR] ratio and they proposed to have the general formulae $[MCl_2(L)_2(H_2O)_2]\cdot nH_2O$ [M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II); $n = 0$–2] and $[FeCl_2(HL)(H_2O)_3]Cl\cdot H_2O$.

3.3. Molar conductance measurements

Table 1 shows the molar conductance values of the complexes. It is concluded from the results that, the divalent metal chelates are found to have molar conductance values of 13.75–18.60 Ω^{-1} mol^{-1} cm^2 indicating their non ionic nature and they considered as non-electrolytes. The Fe(III) complex is found to have a molar conductance value of 75.50 Ω^{-1} mol^{-1} cm^2 indicating its electrolytic nature and of the type 1:1 electrolyte.

3.4. IR spectral studies

The data of the IR spectra of SPR ligand and its complexes are listed in Table 2. The IR spectra of the complexes are compared with the free drug in order to determine the coordination sites that may be involved in chelation. Upon comparison it is found that:

The $\upsilon_{asym}(SO_2)$ and $\nu_{sym}(SO_2)$ stretching vibrations are found in the free SPR ligand at 1344 and 1089 cm^{-1}. Although these bands are not involved in chelation, the shift of these bands to higher or lower wavenumbers in the complexes may be attributed to the