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Synthesis, spectroscopic, thermogravimetric and antimicrobial studies of mixed ligands complexes

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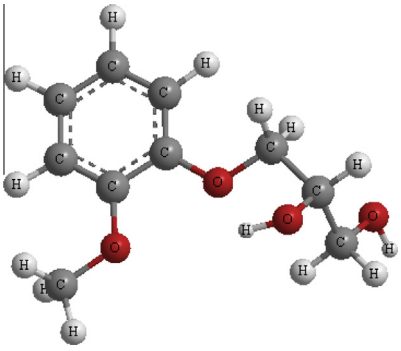
HIGHLIGHTS

- Synthesis of mixed ligand complexes of guaifenesin and glycine in 1:1:1 molar ratio.
- Guaifenesin acts as monobasic tridentate while electronic and magnetic data proposed an octahedral geometry.
- HF method with 3-21G basis set is used to investigate the molecular structure of GFS ligand.
- The antibacterial activity was screened of the compounds.
- The complexes exhibit considerable anticancer activity against the breast cell line (MFC7).

GRAPHICAL ABSTRACT

Geometry optimized structures of GFS.



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ABSTRACT

An interesting series of mixed ligand complexes have been synthesized by the reaction of metal chloride with guaifenesin (GFS) in the presence of 2-aminoacetic acid (HGly) (1:1:1 molar ratio). The elemental analysis, magnetic moments, molar conductance, spectral (UV–Vis, IR, ^{1}H NMR and ESR) and thermal studies were used to characterize the isolated complexes. The molecular structure of GFS is optimized theoretically and the quantum chemical parameters are calculated. The IR showed that the ligand (GFS) acts as monobasic tridentate through the hydroxyl, phenoxy etheric and methoxy oxygen atoms and co-ligand (HGly) as monobasic bidentate through the deprotonated carboxylate oxygen atom and nitrogen atom of amino group. The molar conductivities showed that all the complexes are non-electrolytes except Cr(III) complex is electrolyte. Electronic and magnetic data proposed the octahedral structure for all complexes under investigation. ESR spectrum for Cu(II) revealed data which confirm the proposed structure. Antibacterial screening of the compounds were carried out in vitro on gram positive (*Bacillus subtilis* and *Staphylococcus aureus*), gram negative (*Escherichia coli* and *Neisseria gonorrhoeae*) bacteria and for in vitro antifungal activity against *Candida albicans* organism. However, some complexes showed more chemotherapeutic efficiency than the parent GFS drug. The complexes were also screened for their in vitro anticancer activity against the breast cell line (MFC7) and the results obtained showed that they exhibit a considerable anticancer activity.

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Introduction

Guaifenesin remains the only expectorant approved by the United States Food and Drug Administration (FDA) [1]. Despite its availability and common usage for decades, few studies have evaluated the antitussive effect of guaifenesin. A recently published trial demonstrated the ability of guaifenesin to inhibit cough-reflex sensitivity in subjects with acute URI, thus suggesting an antitussive as well as expectorant action for the drug [2].

Mixed ligand complexes play an important role in biological process as exemplified by many instances in which enzymes are known to be activated by metal ions [3–9]. Also, amino acids as co-ligand have special importance compared to other chemical compounds in the sense that they are regarded as the foundation stones of living organisms. Fostered by the crucial role of amino acids in our life, studying their structural, chemical and physical properties becomes very necessary to explain their behavior and potential applications [10].

The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance. Metal complexation is a process by which certain inorganic metal ions coordinate with organic functional groups through ionic bonds, and ion dipole interactions to form organometallic hybrids having many interesting properties and applications [11–13].

The present study describes the coordination behavior of guaifenesin (GFS) (Fig. 1) in the presence of 2-aminoacetic acid (co-ligand) towards some metal ions. The structure of the isolated metal complexes is elucidated using elemental analyses, IR, ESR spectra, molar conductance, magnetic susceptibility and thermal analyses measurements. Antibacterial and anticancer activity for ligands and its M(II)/(III) complexes were investigated.

Experimental

Material and reagent

All chemicals used were of the analytical reagent grade (AR), and of highest purity available. The chemicals used included guaifenesin drug which was supplied from National Organization for Drug Control and Research, $CrCl_3{\cdot}6H_2O$ and $MnCl_2{\cdot}2H_2O$ (Sigma), $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$ and $ZnCl_2{\cdot}2H_2O$ (BDH), $FeCl_3{\cdot}6H_2O$ (Prolabo), $CdCl_2{\cdot}2H_2O$ and glycine (The drug houses B.D.H laboratory chemicals division poole, England). Organic solvents were spectroscopic pure from BDH included ethanol, diethyl ether and dimethyl formamide. Hydrogen peroxide, sodium chloride, sodium carbonate and sodium hydroxide (A.R.) were used. Human tumor cell line (Breast cell) was obtained frozen in liquid nitrogen (−180 °C) from the American Type Culture Collection. The tumor cell line (MCF7) was maintained in the National Cancer Institute, Cairo, Egypt, by serial sub-culturing.

A fresh stock solution of 1×10^{-3} M of GFS (0.4 g/L) was prepared in the appropriate volume of absolute ethanol and DMF by a ratio (1:3 v/v Ethanol:DMF). Dimethylsulphoxide (DMSO) (Sigma Chemical Co., St. Louis, Mo, USA): It was used in cryopreservation of cells. RPMI-1640 medium (Sigma Chemical Co., St. Louis, Mo, USA) was used. The medium was used for culturing and maintenance of the human tumor cell lines. The medium was supplied in a powder form. It was prepared as follows: 10.4 g medium was weighed, mixed with 2 g sodium bicarbonate, completed to 1 L with distilled water and shaked carefully till complete dissolution. The medium was then sterilized by filtration in a Millipore bacterial filter (0.22 μm). The prepared medium was kept in a refrigerator (4 °C) and checked at regular intervals for contamination. Before use the medium was warmed at 37 °C in a water bath and the supplemented with penicillin/streptomycin and FBS.

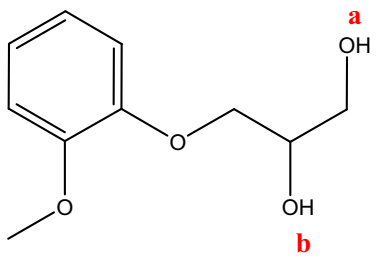

Fig. 1. Structure of ligand (GFS).

The chemicals used (Sodium bicarbonate was used for the preparation of RPMI-1640 medium, 0.05% isotonic Trypan blue solution was prepared in normal saline and was used for viability counting, 10% Fetal Bovine Serum (FBS) (heat inactivated at 56 °C for 30 min), 100 units/ml Penicillin, 2 mg/ml were used for the supplementation of RPMI-1640 medium prior to use, 0.025% (w/v) Trypsin was used for the harvesting of cells, 1% (v/v) Acetic acid was used for dissolving the unbound SRB dye, 0.4% Sulphorhodamine-B (SRB) dissolved in 1% acetic acid was used as a protein dye and A stock solution of trichloroacetic acid (TCA) 50%, was prepared and stored where 50 μl of the stock was added to 200 μl RPMI-1640 medium/well to yield a final concentration of 10% used for protein precipitation. 100% Isopropanol and 70% ethanol were used. Tris base 10 mM (pH 10.5) was used for SRB dye solubilization. 121.1 g of tris base was dissolved in 1000 ml of distilled water and pH was adjusted by HCl acid (2 M)) were of supplied from Sigma Chemical Co., St. Louis, Mo, USA.

Measurements

Microanalyses of carbon, hydrogen and nitrogen were carried out at the Microanalytical Center, Cairo University, Egypt, using CHNS-932 (LECO) Vario Elemental Analyzer. Analyses of the metals followed the dissolution of the solid complex in concentrated HNO_3, neutralizing the diluted aqueous solutions with ammonia and titrating the metal solutions with EDTA. FT-IR spectra were recorded on a Perkin–Elmer 1650 spectrometer (4000–400 cm^{-1}) in KBr discs at room temperature. The diffused reflectance spectra on solid complexes were recorded at room temperature on a Shimadzu 3101pc spectrophotometer. The spectrophotometric measurements were carried out at room temperature using the manual Unico 1200 (United Products and Instruments, Inc.) in the wavelength range from 325–1000 nm with 1 cm quartz cell and effective band width 1 nm. ^1H NMR spectra, as a solution in DMSO-d_6, were recorded on a 300 MHz Varian-Oxford Mercury at room temperature using TMS as an internal standard. Electron spin resonance spectra were also recorded on JES-FE2XG ESR spectrophotometer at Microanalytical Center, Tanta University.

Mass spectra were recorded by the EI technique at 70 eV using MS-5988 GS–MS Hewlett–Packard instrument at the Microanalytical Center, National Center for Research, Egypt. The molar magnetic susceptibility was measured on powdered samples using the Faraday method. The diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant Molar conductivities of 10^{-3} M solutions of the solid complexes in DMF were measured on the using Jenway 4010 conductivity meter. The thermogravimetric analyses (TG and DTG) of the solid complexes were carried out from room temperature to 800 °C using a Shimadzu TG-50H thermal analyzer. The X-ray powder diffraction analyses were carried out by using Philips Analytical X-ray BV, diffractometer type PW 1840. Radiation was provided by copper target (Cu anode 2000 W) high intensity X-ray tube operated at 40 KV and 25 mA. Divergence and the receiving slits