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Synthesis, structural characterization and biological studies of some nalidixic acid–metal complexes: Metalloantibiotic complexes of some divalent and trivalent metal ions

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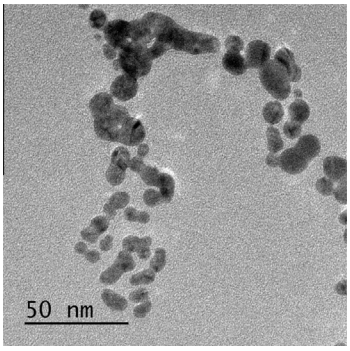
HIGHLIGHTS

- Some divalent and trivalent complexes of nalidixic acid were discussed.
- Structures of complexes were fully spectroscopic characterizations.
- Nalidixic acid reacts as a bidentate ligand.
- The gold(III) complex has nano-scale range.
- Anticancer activity was checked.

GRAPHICAL ABSTRACT

TEM image of $[Au(nix)(Cl)_2]$ complex.



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ABSTRACT

This article describes the synthesis, characterization, computational and biological assessments of some divalent and trivalent metal (Ca(II), Fe(III), Pd(II) and Au(III)) complexes of nalidixic acid (nixH). The structures of these complexes were assigned using elemental analyses and spectral measurements e.g., IR, Raman, ^{1}H NMR, ^{13}C NMR and electronic techniques. These results indicated that, nalidixic acid reacts as a bidentate ligand bound to the metal ion through the oxygen atoms of carbonyl and carboxylate groups. The molar conductance measurements of the complexes in DMSO correspond to be non-electrolyte nature. Thus, these complexes may be formulated as $[Ca(nix)(Cl)(H_2O)_3].H_2O$, $[Fe(nix)(Cl)_2(H_2O)_2]\cdot 3H_2O$, $[Pd(nix)(Cl)(H_2O)]$ and $[Au(nix)(Cl)_2]$. Base on the Coats–Redfern and Horowitz–Metzeger methods, the kinetic thermodynamic parameters (E^*, ΔS^*, ΔH^* and ΔG^*) of the thermal decomposition reactions have been calculated from thermogravimetric curves of TG and DTG. The nano-scale range of the nalidixic acid complexes have been discussed using X-ray powder diffraction (XRD), scanning electron microscope (SEM) and transmission electron microscopy (TEM) analyzer. The computational studies for the synthesized complexes have been estimated.

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Introduction

Nalidixic acid (nixH, Fig. 1) was commonly named as 1-Ethyl-1, 4-dihydro-7-methyl-4-oxo-1,1,8-naphthyridine-3-carboxylic acid and its belongs to a 4-quinolone antibiotic drug families. The 4-quinolones is a class of antibacterial agents which has been known for over 40 years [1]. Quinolones were comprised of a large family of antibacterial agents such as nalidixic acid, perfoxacin, norfloxacin, ofloxacin, and ciprofloxacin. Some of fluoroquinolones and their derivatives have been used in the improvement of antimicrobial, anticancer, anti-inflammatory, antiviral, and anti-HIV activities [2–4].

Nalidixic acid has been used in the treatment of several diseases as a powerful antibiotic drug for decontamination of the gut infections [5–12].

The different metal ions constituted the backbone for the metalloantibiotic skeletons, which were helpful to enhancement of biological and medical functions [13–17]. Metalloantibiotics interact with DNA, RNA, proteins, receptors and lipids, making them very unique and specific. Metal contamination potentially contributes to the maintenance and spread of antibiotic resistance factors. Antibiotics metal complexes as well as mixed antibiotics metal complexes were found more effective as chemotherapy agents than their parent antibiotics [13–18].

Quinolones drugs are good complexing agents for different transition and non-transition metal ions. The synthesis and characterization of metal complexes with quinolone antibacterial agents were of great importance for understanding the drug-metal ion interaction and for their potential pharmacological usage [18,2,3]. Precise dissociation constants as well as stability constants for the binding of the nalidixate anion using several divalent metal ions were reported [19]. Nakano et al. [20] have been reported the ability of nalidixic acid drug to form complexes with aluminum(III), magnesium(II) and calcium(II) ions. Complex formation between nalidixic acid, metal ion and DNA has been discussed [21]. Behrens et al. have been synthesized and characterized the transition metal complexes of nalidixic acid. The nalidixic acid was used in the clinical treatment of urinary tract infections caused by gram-negative bacteria. The mode of coordination of the drug was investigated by spectroscopic studies. From the spectral data, nalidixic acid anion binds through the carboxylate group either as a chelate or as bridge to give polymeric structure [22]. The most metal complexes of fluoroquinolone prefer to coordinate as bi-dentate statement ligand- to- metal through the carbonyl and one oxygen atoms of the carboxylic group. The antimicrobial activities of these complexes were greater than free ligand against the tested organisms [16–20]. The studied metal complexes of fluoroquinolones have the potential of being used as drugs. The chemistry of metal-drug coordination compounds is more popular now than before in importance particularly in the design of more biologically active drugs [23]. Metal ions are known to affect the action of many drugs. The efficacies of the drugs on coordination with a metal are enhanced in many cases [24]. Metal ions play an essential role in a vast number of widely differing biological processes and depending on their concentration, they may either contribute toward the health of the organism or cause toxicity [25,13]. In literature survey, the great attention has been drawn to studies of the antitumor activities of inorganic especially metal complexes [26,27]. The transfer of metal ion from the ligand to the viruses associated with cancer is a mechanism for releasing the anticancer drug in the locality of the tumor [27].

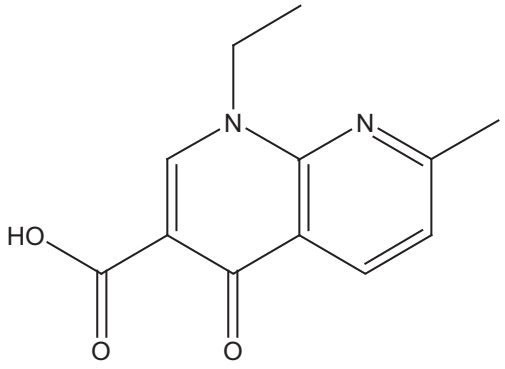

Fig. 1. Nalidixic acid (1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,1,8-naphthyridine-3-carboxylic acid) free drug.

For the continuation of the methodology for our research group, this deals with metal-drug interactions [28–33]. Metal ions play an essential role in the design of more biologically active drugs, so, this article aimed to synthesis, theoretical calculations, spectroscopic characterizations, thermal stabilities and their biological evaluations of new nalidixic complexes with some of divalent and trivalent metal ions (Ca(II), Fe(III), Pd(II) and Au(III)). The experimental studies have been accompanied by theoretical calculations (PM3) due to their important role in understanding of the probably behavior of the compound during reactions and identification of the important information about the compounds under investigations, like total energy, binding energy, electronic energy, dipole moment, bond lengths, LUMO and HOMO.

Experimental

Chemicals

Nalidixic acid mentioned in this article was received from the Aldrich chemical company. All of chemicals used for this study were of analytically reagent grade, commercially available from BDH and used without previous purification like $CaCl_2$, $FeCl_3{\cdot}6H_2O$, $PdCl_2$ and sodium tetrachloroaurate(III) dehydrate ($NaAuCl_4{\cdot}2H_2O$).

Synthesis

The Ca(II), Fe(III), Pd(II) and Au(II) nalidixate complexes were prepared by refluxing 1:1 M ratio for the mixture of the nixH ligand (1 mmol) with each metal chloride salt in methanolic medium on a hotplate for 2–3 h at ~70 °C. The precipitate was filtered off washed with methanol and diethyl ether and finally dried in a vacuum desiccator's over anhydrous calcium chloride. The yields of the final products were 70–75%.

Instruments

Carbon, hydrogen and nitrogen analyses have been carried out in Vario EL Fab. CHNS. The amount of water and the metal content percentage were determined by gravimetric analysis method. Infrared spectra of the nix complexes were recorded on Bruker infrared spectrophotometer in the range of 400–4000 cm^{-1}, while Raman laser spectra of samples were measured on the Bruker FT-Raman with laser 50 mW. The molar conductances of 10^{-3} M solutions of the complexes in DMSO solvent were measured on a HACH conductivity meter model. All the measurements were taken at room temperature for freshly prepared solutions. The electronic spectrum of the complexes were measured in DMSO solvent with concentration of 1×10^{-3} M, in rang 200–800 nm by using Unicam UV/Vis spectrometer. The mass susceptibility (X_g) of complexes was measured at room temperature using Gouy's method by a magnetic susceptibility balance from Johnson Metthey and