Journal of Molecular Structure 1130 (2017) 264–275

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Structural and chelation behaviors of new Ru(II), Pt(IV) and Ir(III) gatifloxacin drug complexes: Spectroscopic characterizations

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ARTICLE INFO

Article history:
Received 23 August 2016
Received in revised form
6 October 2016
Accepted 9 October 2016
Available online 11 October 2016

Keywords:
Gatifloxacin
Electronic spectra
Chelation
Ruthenium
Iridium
Platinum

ABSTRACT

The interaction between gatifloxacin drug (GAT) with some transition metals (Ru(III), Pt(IV) and Ir(III)) yield the complexes of formulas $[Ru(GAT\text{-}NH_4)(Cl)_3(H_2O)_2]$, $[Pt(GAT\text{-}NH_4)_2(Cl)_4]\cdot 3H_2O$ and $[Ir(GAT\text{-}NH_4)_2(Cl)_2(H_2O)_2]\cdot Cl\cdot 2H_2O$ at pH = 7–8. The composition of the GAT complexes was confirmed by elemental data. The IR frequencies reveal the coordination of the GAT with metal ions and the coordination mode of the –N atom of 3-methylpiperazinyl moiety to metal. XRD pattern show isomorphism among the complexes with similar chelation behavior. Scanning electron microscope (SEM) and transmission electron microscopy (TEM) were used to identify the particle size of GAT complexes. The thermal data reveals that various steps of decomposition of the complexes to form their metal oxide as final product. The electronic spectra and the magnetic susceptibility values reveal that the coordination and geometry of Ru^{3+}, Pt^{4+} and Ir^{3+} complexes possess distorted octahedral geometry with six number of coordination. Thermodynamic parameters (E^*, ΔS^*, ΔH^* and ΔG^*) were calculated from TG curves dependent on Coats–Redfern and Horowitz–Metzeger non–isothermal methods.

1. Introduction

The GAT drug has an IUPAC name, (±)–1-cyclopropyl-1,4-dihydro-6- fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3- quinolinecarboxylic acid (GAT; Fig. 1), is a good antibacterial agent that has a wide spectrum of bacterial activity against aerobic and anaerobic [1]. As a member of the fluoroquinolone family compounds, GAT is a 4th generation with specific inhibitor for bacterial DNA-gyrase [2]. The characteristic of substituted piperazine ring at 7-position and methoxy group at 8-position of the quinolone ring play an important roles in the biological process [3,4] and the carbonyl and carboxyl groups of quinolone ring provide coordination sites for metal ions. The research on metal complexes of quinolones has attracted much attention due to their improved solubility in water [5] or enhanced the fluorescence properties [6–12] and their biological activities have been reported in literature [13–16]. The chelation of metal ions with different drugs is an essential subject in the field of inorganic chemistry and biology [17,18] and in some cases the highest activity of a drug is associated with a metal atom [19–23]. The metal oxidation state, the type and number of donor atoms, as well as their relative positions within the ligand are major factors determining the relationship between structure and activity [19–23].

Quinolone antibiotics can participate in the formation of complexes in a number of ways [24–28]. In case of isolated these complexes in acidic media usually contain singly and/or doubly protonated quinolones that are in capable of bonding to the metal ion and in these cases only electrostatic interaction was observed between the drug and the metal ions [24–26]. On the other hand [27–29] it was found that neutral quinolones in the zwitterionic state are capable of forming simple complexes (bidentate chelating). The quinolones can also act as bridging ligands and thus capable of forming polynuclear complexes [28,29]. Rarely, quinolones can be acts as bi–dentate chelate via two carboxyl oxygen atoms or through both piperazinic nitrogen atoms. Quinolones can also form complexes as uni–dentate ligand binding to the metal ion through terminal piperazinyl nitrogen [30].

The medicinal usage of platinum(II,IV) compounds was limited by the development of tumor resistance to the drugs [31,32] and by their side effects [33]. These limitations caused further research to

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http://dx.doi.org/10.1016/j.molstruc.2016.10.036
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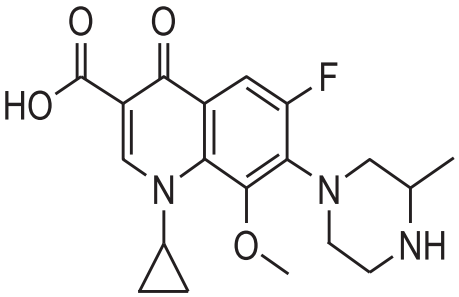

Fig. 1. Structure of GAT drug.

be oriented toward finding new, more active, less toxic anti-tumor agents based on other chelates. Ruthenium(III) complexes had shown ligand exchange kinetics similar to those of the platinum anti-tumor agents currently used in the clinic and exhibits a reduced toxicity [34,35].

This paper focused on the preparation, spectroscopic and thermal stability characterizations of Ru(III), Pt(IV) and Ir(III) complexes with GAT as a 4th generation of quinolone drugs. In the present work, three novel ruthenium(III), platinum(IV) and iridium(III) GAT complexes have been synthesized and structurally characterized by micro–analytical, FT–IR, conductance, magnetic, UV–vis, ^{1}H NMR and TG–DTG analyses. The morphological surface and particle size of these three new complexes was investigated by using XRD, SEM and TEM.

2. Experimental

2.1. Chemical materials

GAT drug was purchased from Aldrich–Sigma Chemical Company. The $RuCl_3$, $H_2PtCl_6{\cdot}6H_2O$ and $IrCl_3{\cdot}{\cdot}xH_2O$ and solvents like (CH_3OH and dimethylformamide (DMF)) were purchased from Fluka Chemical Company and used without further purification.

2.2. Synthesis of GAT complexes

A hot methanolic solution (2 mmol, 20 mL) of GAT (0.752 g) was added to an aqueous solution (1 mmol, 20 mL) of $RuCl_3$ (0.208 g), ($H_2PtCl_6{\cdot}6H_2O$ (0.518 g) and $IrCl_3{\cdot}$ xH_2O (0.299 g), the reaction mixtures were neutralized at pH = 7–8, then refluxed for 2–3 h at ~60–70 °C. The solutions were filtered off and left for slow evaporation over night. After a one day left a dark green, yellowish brown and yellow solid powder precipitations of the Ru(III), Pt(IV) and Ir(III) GAT complexes, respectively, were deposited, collected with filtration, washed with methanol and dried under vacuum. The addition of an aqueous ammonia solution to neutralized the GAT complexes mixtures make to formation of an ammonia–based complex.

2.2.1. [Ru(GAT–NH_4)$(Cl)_3(H_2O)_2$] (**1**) complex

Yield: 0.77 g, 80%. Anal. Calc. for complex (**1**) ($C_{19}H_{29}Cl_3FN_4O_6Ru$) (MW = 635.88 g/mol): Calcd.: C, 35.89; H, 4.60; N, 8.81. Found: C, 35.44; H, 4.53; N, 8.69%. The complex is dark green color, soluble in (DMSO and DMF) and is a non-electrolyte (0.021 mS).

2.2.2. [Pt(GAT–NH_4)$_2(Cl)_4]{\cdot}3H_2O$ (**2**) complex

Yield: 0.92 g, 72%. Anal. Calc. for complex (**2**) ($C_{38}H_{56}Cl_4F_2N_8O_{11}Pt$) (MW = 1175.79 g/mol): Calcd.: C, 38.82; H, 4.80; N, 9.53. Found: C, 38.30; H, 4.69; N, 9.06%. The complex is yellowish brown, soluble in (DMSO and DMF) and is a non-electrolyte (0.026 mS).

2.2.3. [Ir(GAT–NH_4)$_2(Cl)_2(H_2O)_2]{\cdot}Cl{\cdot}2H_2O$ (**3**) complex

Yield: 0.89 g, 85%. Anal. Calc. for complex (**3**) ($C_{38}H_{58}Cl_3F_2IrN_8O_{12}$) (MW = 1155.49 g/mol): Calcd.: C, 39.50; H, 5.06; N, 9.70. Found: C, 39.12; H, 4.96; N, 8.96%. The complex is yellow color, soluble in (DMSO and DMF) and is a slightly electrolyte (0.124 mS) with one chlorine atom existed outside the coordination sphere.

2.3. Instrumentations and analytical measurements

The micro-analytical analyses of %C, %H and %N percentages were determined using a Perkin Elmer CHN 2400. The amount of water and the metal content percentage were determined by gravimetric analysis method. The molar conductivities of GAT complexes with 10^{-3} mol/cm^3 concentration in DMSO solvent were measured using Jenway 4010 conductivity meter. The UV–vis absorption spectra were recorded in DMF solvent within 200–800 nm using a UV2–Unicam UV/Vis Spectrophotometer fitted with a quartz cell of 1.0 cm path length. The infrared spectra with KBr discs were recorded on Bruker FT–IR Spectrophotometer (4000–400 cm^{-1}). The thermal studies TG/DTG were carried out on a Shimadzu TGA–50H thermal analyzer. All experiments were performed using a single loose top loading platinum sample pan under nitrogen atmosphere at a flow rate of 30 mL/min and a 10 °C/min heating rate for the temperature range 25–800 °C. ^{1}H NMR spectra were recorded as DMSO solutions on a Bruker 600 MHz spectrometer using TMS as the internal standard. SEM images were obtained using a Jeol Jem–1200 EX II Electron microscope at an acceleration voltage of 25 kV. X-ray diffraction (XRD) patterns of the samples were recorded on X Pert Philips X-ray diffractometer. All the diffraction patterns were obtained by using $CuK_{\alpha 1}$ radiation, with a graphite monochromator at 0.02°/min scanning rate. The transmission electron microscopy images were performed using JEOL 100s microscopy. The mass susceptibility (X_g) of complexes was measured at room temperature using a Gouy magnetic balance. The effective magnetic moment (μ_{eff}) value was obtained using the following equations (1)–(3)[36].

$$X_g = \frac{C_{Bal}L(R - R_0)}{10^9 M} \quad (1)$$

Where:

R_o = Reading of empty tube
L = Sample length (cm)
M = Sample mass (gm)
R = Reading for tube with sample
C_{Bal} = balance calibration constant = 2.086

$$X_M = X_g x\ M.Wt. \quad (2)$$

The values of X_M as calculated from equation (2) are corrected for the diamagnetism of the ligand using Pascal's constants, and then applied in Curie's equation (3).

$$\mu_{eff} = 2.84\ \sqrt{X_M x\ \ T} \quad (3)$$

Where T is temperature in Kelvin.

2.4. Molecular modeling studies

The theoretical data of quantum chemical of the GAT drug