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Original article

Identification of pharmacophore in bioactive metal complexes: Synthesis, spectroscopic characterization and application

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ABSTRACT

Bacteria are amongst the most adaptable organisms on the Earth. The year 2010 was always remarkable for the article published in Lancet Infection Disease by Kumarasamy et al. and the enzyme NDM-1 which makes bacteria resist designed to kill them. Four rhodium(III) chloride complexes with Gatifloxacin have been prepared and characterized by elemental analyses, molar conductance measurements, FTIR, FAB-MS, TGA, ^{1}H NMR and electronic spectral studies. The general formula for complexes are $[X]^+$ *fac*-$[RhCl_3(L)(GT)]^-$; where L = H_2O, Dimethylsulfoxide (DMSO), Tetramethylenesulfoxide (TMSO); GT = Gatifloxacin and X = Na or $[H(DMSO)_2]$. All complexes are found to possess prominent antibacterial activity against pathogenic *Escherichia coli* and *Mycobacterium tuberculosis* in comparison to Gatifloxacin.

1. Introduction

Discovery of antibiotics at the beginning of 20th century and their spectacular success in combating infections and deaths; created complacency during 1960s and 1970s. Over the past six decades, these ‘wonder drugs’ have played a critical role in reducing global burden of communicable diseases. This success was however overshadowed by the rapid backlash of microbes resulting in a “relentless and dizzying rise of antimicrobial resistance” [1,2]. The year 2010 will surely be remembered because in this year extensively drug-resistant bacteria attracted global attention. The gene for NDM-1 (New Delhi Metallo Beta-Lactamase-1) produces an enzyme which makes bacteria resistant to most antibiotics including **fluoroquinolones**, aminoglycosides and beta-lactams [3]. Fluoroquinolones (FQs) are a class of compounds which widely used as broad-spectrum antimicrobial agent [4]. In last few years these molecules have notice from interdisciplinary areas of scientific community due to both practical purposes and fundamental aspects. Gatifloxacin (GT) is a fluoroquinolone with a methoxy side chain at the C-8 position that not only seems to increase bactericidal action, enhance the ability of drug; to inhibit growth of mutants but also reduces the quinolone associated phototoxicity [5–8].

Uses of metal in medicines have become increasingly important over the last couple of decades resulting in a variety of exciting and valuable drugs [9–12]. The metal complexes are amenable to combinatorial synthetic methods, and an immense diversity of structural scaffolds can be achieved. Metal centers are capable of organizing surrounding atoms to achieve pharmacophore geometries that are not readily achieved by other means. The toxic properties of compounds were related to chemical structure and specifically to particular substructures, called toxicophores. In designing novel bioactive molecule, if toxicophore for efficacy is must, then corresponding detoxifying substructure should be identified. Detoxifying substructures can make toxicophore-containing compounds non-mutagenic [13]. Knowledge of chemical functionalities of these toxicophores was identified by chemists. Thus, with this aim the study is an attempt to compare metal toxicity in surrounding with suitable pharmacophore. With this view, we have synthesized Gatifloxacin rhodium(III) chloride derivative with or without sulfoxide ligand, in anticipating better reactivity in resulting compounds against *Escherichia coli* and *Mycobacterium tuberculosis*.

2. Results and discussion

The complex **1** was synthesized by reaction between Gatifloxacin (GT) and hydrated rhodium trichloride and **2**–**4** were obtained in reaction of selected rhodium(III) sulfoxide precursor and

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GT in acetone. The desired product is formed as solids on vacuum evaporation.

Empirical formula of complexes **1**–**4** were in good agreement with elemental analyses. Reactions involved in formation of **2**–**4** are well-known substitution reaction. Molecular weight was determined by FAB-MS, where pseudo molecular ion peak was appeared. The higher values of molar conductance in DMSO for complexes **1**–**4** were indicating their ionic nature [14,15].

2.1. Infrared spectral analysis

GT coordinated to metal ion in a bidentate manner *via* carboxylic and carbonyl oxygen and formed six-member stable ring chelate. Disappearance of band ~1700 cm^{-1} due to free carboxylic group in **1**–**4**, indicates involvement of carboxylic oxygen in coordination. In FTIR spectra of complexes two absorption bands around 1600 and 1400 cm^{-1} were observed due to asymmetric and symmetric mode of ν (COO^-), respectively. The carboxylate group can bind to metal ions in a monodentate, bidentate or bridging manner [16]. The frequency difference [$\Delta\nu = \nu_{as}(COO^-) - \nu_s(COO^-)$] can be used as an indication of binding mode of the carboxylate ion (Table 1). If $\Delta\nu > 200$, this group is probably bound in a monodentate fashion [17], as it was observed for complexes **1**–**4** reported herein. Strong absorption band for C=O, appears at frequency lower than 1600 cm^{-1} in FTIR spectra of all complexes, suggesting coordination of GT to metal through oxygen atom of carbonyl group [18]. Appearance of ν (Rh–O) band near 450 cm^{-1}, also confirms our view [19].

In complex **1**, a broad absorption band centered at 3432 cm^{-1}, was due to –OH stretching, indicating the presence of water molecule [20]. The band observed at 822 cm^{-1} assigned for rocking mode for coordinated water, also confirms this view [16]. Disappearance of band in region 929 and 928 cm^{-1}, in complex **2** and **4**, assigned for ν (DMSO-*O*) and ν (TMSO-*O*), respectively [21], indicating its substitution with GT. However in **2**–**4**, the band observed in between 1140 and 1156 cm^{-1}, due to ν (SO-*S*). Absorption band for ν (Rh–S) was observed near 420 cm^{-1} and for ν (Rh–Cl), two stretching modes were appeared as intense band in between 333 and 358 cm^{-1}. This data is in consistent with *fac*-configuration [21,22]. In complex **3** a broad band appeared at 752 cm^{-1} along with a sharp band at 862 cm^{-1} assigned for free DMSO, indicating the presence of hydrogen bonded DMSO [21,23].

2.2. Electronic spectral analysis

Complexes **1**–**4** were diamagnetic (low spin d^6, $S = 0$), as expected for low spin Rh(III) compounds. Five bands were observed in electronic spectra. In visible region three broad bands with low extinction coefficient were observed in between 688 and 681, 548 and 542 and 409 and 403 nm, assigned for transition $^1A_1g \rightarrow {}^3T_1g$, $^1A_1g \rightarrow {}^1T_1g$ and $^1A_1g \rightarrow {}^1T_2g$ of Rh(III) [21]. However, higher energy absorption bands below 340 nm was attributed to $\pi \rightarrow \pi^*$ intraligand transition in coordinated π-acidic imine ligand [24–27]. In complex **3**, a weak absorption band at about 300 nm was probably due to protonated sulfoxide cation [24–27].

Table 1
Stretching vibrations for carboxylate ion in IR spectrum (in cm^{-1}).

Compounds	$\nu_{as}(COO)^-$	$\nu_s(COO)^-$	$\Delta\nu^a$
1	1614	1384	230
2	1623	1396	227
3	1626	1398	228
4	1620	1382	238

[a] $\Delta\nu = [\nu_{as}(COO)^- - \nu_s(COO)^-]$.

2.3. NMR spectral studies

NMR study for complexes **1**–**4** was not found very helpful, since only small swing in chemical shift values were reported. However, in ^1H NMR spectra of GT, the down field signal about δ 11.00 ppm, due to carboxylic proton [28] was found disappear in all complexes; indicating deprotonation of –COOH group and involvement of carboxylate oxygen in complexation.

A sharp singlet in complex **1**, observed at δ 4.86 ppm for two protons was due to coordinated water. In complex **2** and **3**, singlet appeared at δ 3.58 and δ 3.55 ppm was assigned for six DMSO-*S* protons, respectively. However, signal centered at δ 2.72 ppm for twelve protons in complex **3**, was due to free DMSO. In complex **4**, the multiplet at δ 4.18 and δ 2.32 ppm (for four protons) was assigned for $S–CH_2$ and $S–C–CH_2$, respectively [14,21,23].

2.4. Thermal analysis

Thermal analysis gives information about the stability of metal chelates and decides to some extent whether water molecules are inside or outside of coordination sphere. TGA curve of complex **1** show three weights losses; first in range 110–140 °C, due to loss of one coordinated water molecule. However second loss was at 272 °C, correspond to three chloride ions and total decomposition of complex occurs at 404–530 °C [19,29].

In complex **2**–**4**, decomposition involved in two steps: first step indicated loss of three chloride ions in temperature range 280–300 °C, while second loss was observed at 350–450 °C range giving residue. At final steps the end products stable metal oxide as Rh_2O_3 was found at 680–720 °C [19,29]. Absence of an endothermic peak in complexes **2**–**4**, confirmed that these complexes were not hydrated.

2.5. Structure of complexes 1–4

In complex **3**, it was evident on the basis of electronic and FTIR spectra; that probably one Cl, from precursor $[\mathbf{H(DMSO)_2}]^+$ ***trans*-**$[\mathbf{RhCl_4(DMSO\text{-}\mathit{S})_2}]^-$ is replaced [30], along with H^+ ion of –COOH group which is also verified qualitatively by silver nitrate test. Thus binding of GT with metal ion is concluded on the basis of above discussion and results obtained. We proposed *fac*-structure for complexes **1**–**4** (Fig. 1).

3. Antibacterial screening

The complexes **1**–**4** and precursors **1a**–**4a** were screened for antibacterial properties against gram negative bacteria *E. coli*, MTCC 1304 and *M. tuberculosis*, ATCC 27294. Muller Hinton agar plates (MHA) were prepared and 50 μL suspensions of bacterial strains containing approximately 10^5 CFU (Colony Forming Unit) were applied to plate by the Well Diffusion method [31,32]. The deep well was made on plates and then it filled with 50 μL of sample solution. The 0.2 μg/mL solution of Gatifloxacin, DMSO and TMSO were used for comparison. These plates were now incubated at 37 ± 1 °C for 24–48 h in refrigerated incubator shakers. Results were obtained in the form of inhibition zone, which were measured in mm (Table 2).

All complexes **1**–**4** are found active in comparison to GT, probably due to enhanced lipophilicity of complexes, which leads to breakdown of permeability barrier of cell and block the binding site in enzyme of micro organisms, thus retard normal cell process in bacteria and affects their growth [33].