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ANTI-OXIDANT ACTIVITY OF NOVEL METAL COMPLEXES WITH GATIFLOXACIN

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ABSTRACT

Three novel metal complexes of gatifloxacin $[Cu(gtfl)_2(H_2O)_2]$, $[Zn(gtfl)_2]$ and $[VO(gtfl)_2]$ (where ,Gtfl=gatifloxacin) have been prepared. These complexes were characterized by IR, UV-VIS, EPR, NMR spectra. In all complexes, gatifloxacin acts as a bidentate ligand bound to the metal through the pyridone and carboxylate oxygen atoms. The gatifloxacin and their metal complexes have been screened for in-vitro antioxidant activity by using DPPH radical and superoxide dismutase scavenging activities. All metal compounds showed strong antioxidant activities than free ligand gatifloxacin. The obtained IC_{50} value of the DPPH activity for zinc gatifloxacin complex 4 (IC_{50} =3.5µM) was shown to be the best.

Keywords: Gatifloxacin; Metal complexes; Spectroscopy; SOD; DPPH.

1. INTRODUCTION

In recent year there has been a phenomenal increase in literature report on the quinolones antimicrobial agents. These drugs are also referred as Fluoroquinolones, quinolone carboxylic acids and 4-quinolones. They are the analogs of the earlier developed agent Nalidixic acid. The broad-spectrum antibacterial activity was introduced into this class of quinolone compounds through fluorination at C-6 position giving rise to class of compounds which are commonly known as Fluoroquinolones [1]. Since the introduction of the Fluoroquinolones for clinical use in the late 1980 they have been successfully used for the treatment of complicated urinary tract infections, including those caused by *P. aeruginosa*. It is observed that a fluorine atom at C-6 position and a piperazine ring at C-7 position strongly enhance the spectrum of biological activity of these compounds. Such compounds are much more active against aerobic gram-negative microorganisms but less active against gram-positive ones and hence are extremely useful for treatment of a wide variety of infections [2].

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The four-generations of quinolone drugs taking into account their expanded antimicrobial spectrum and clinical indications [3]. Gatifloxacin is a third-generation synthetic broad-spectrum 8-methoxy fluoroquinolone antibacterial drug derivative, which inhibits the bacterial enzymes DNA gyrase and topoisomerase IV. It is active against gram-positive and gram-negative bacteria and also moderate activity against anaerobe and mycobacteria. Gatifloxacin shows excellent pharmacokinetic and pharmacodynamic characters. Bristol-Myers Squibb introduced Gatifloxacin in 1999 under the proprietary name TEQUIN for the treatment of respiratory tract infections, having licensed the medication from Kyorin Pharmaceutical Company of Japan. Allergan produces an eye-drop formulation called Zymar. Gatifloxacin available as tablets and in various aqueous solutions for intravenous therapy [4].Structure of gatifloxacin as shown in **Fig.1** Gatifloxacin is used in the treatment of respiratory tract infection, acute sinusitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, uncomplicated urinary tract infections, uncomplicated urethral and cervical gonorrhea.

Quinolone can form metal complexes with biologically relevant metal; they can be used as Metallodrugs. Recent years have witnessed an unprecedented progress in biological applications of metal coordination compounds of biologically active ligands because of their key role in clinical therapy. Transition metals are particularly suitable for this purpose because they can adopt a wide variety of coordination numbers, geometries and oxidation states in comparison with other main group

elements. One of the characteristics of metals is their potential to undergo redox processes, as determined by their redox potentials. Especially, transition metal ions are usually able to switch between several oxidation states. Due to the redox activity of metals and, therefore, a possible disturbance of the sensitive cellular redox homeostasis, a tight regulation of the metal and redox balance is crucial for health[5].The pharmacological efficiencies of metal complexes depend on the nature of the metal ions and the ligands [6]. It is declared in the literature that different ligands and different complexes synthesized from same ligands with different metal ions possess different biological properties [7,8]. The interactions of quinolones and metal ions have been thoroughly studied especially due to the interesting biological and chemical properties.

In this paper, we present the interaction of the quinolone gatifloxacin with diverse transition metal ions in an attempt to examine the mode of gatifloxacin coordination and biological properties of resulting complexes. Gatifloxacin can usually act as a bidentate ligand through the pyridone oxygen and one carboxylate oxygen. In particular, complexes of gatifloxacin with Cu(II), Vo(II), and Zn(II) have been synthesized and characterized with UV, IR, EPR and NMR spectroscopy. The synthesized compounds have been studied further for their antioxidant activity in vitro.

2. MATERIAL AND METHOD

2.1 Reagents

Gatifloxacin(gtfl) was a purchased from Emcure Pharmaceutical, Pune while all analytical grade chemical like copper chloride ($CuCl_2$), zinc nitrate ($ZnNO_3$), vanadium sulphate ($VOSO_4$), methanol and ethanol were purchased from Sigma Aldrich chemical Mumbai.

2.2 Synthesis

All the complexes are prepared as following with 1:2 ratios (metal: gatifloxacin).

2.2.1 Synthesis of [Cu (gtfl) $_2$.2H_2o (2)]

The Cu (II) complex (2) was synthesized by adding $CuCl_2.2H_2o$ (1mmol), CH_3ONa (1mmol) and (gtfl) (1) (2mmol) in methanol and stirring the reaction mixture for 6 hr yielding a dark green ppt. which was filtered.

2.2.2 Synthesis of [VO (gtfl) $_2$(3)]

The VO complex (7) was synthesized by adding $VOSO_4.XH_2o$ (1mmol), CH_3ONa (1mmol) and (gtfl) (1) (2mmol) in methanol and stirring the reaction mixture for 6 hr yielding a light green ppt. which was filtered.

2.2.3 Synthesis of [Zn (gtfl) $_2$(4)]

The Zn complex (6) was synthesized by adding $ZnNO_3.6H_2o$ (1mmol), CH_3ONa (1mmol) and gtfl (1) (2mmol) in methanol and stirring the reaction mixture for 6 hr yielding a white ppt. which was filtered.

2.3 Physical Measurements

2.3.1. IR spectroscopy

Infrared spectra were recorded as KBr pellets on Shimadzu 8400 infrared spectrophotometer.

2.3.2. Electronic spectroscopy

Electronic absorption spectra were recorded on Shimadzu 1700 UV-VIS spectrophotometer using matched pair of 1 cm^2 quartz cells.

2.3.3 Magnetic susceptibility measurements

Magnetic susceptibility measurements of the synthesized complexes were measured at room temperature on Faraday type magnetic balance in our laboratory with the field strength of 7000G and the molecular susceptibilities were corrected for diamagnetism of the components atoms using Pascal's constants. Mercury (II) tetrathiocyanatocoaltate, Hg [Co (NCS) $_4$] was used as the calibrant.

2.3.4. Electron paramagnetic resonance spectroscopy

The electron spin resonance studies of all the copper complexes were recorded at 100K on a Varian X-band spectrometer at Regional Sophisticated Instruments Center (RSIC), Indian Institute of Technology (IIT) Powai, Mumbai, INDIA. TCNE was used as a field marker (g_{iso} = 2.0028).

2.3.5. NMR spectroscopy

Proton NMR spectra were measured on a Varian instrument of Chemistry Department, University of Pune, Operating at 300 MHz in d^6 – DMSO solvent.

2.4 Antioxidant activity:

2.4.1 *In vitro* inhibition of Superoxide Dismutase Assays:

The SOD like activities of copper complexes were determined by the NBT method in triplicate and are presented as mean percentage inhibition of NBT reduction. The super oxide scavenging activity of the compound was measured using the absorbance of blue formazan produced from the yellow dye NBT 2+.The capacity of the compounds to scavenge the super oxide radical was measured by this assay method Briefly,1ml of tris buffer was taken in a test tube, to this 0.5 ml of NBT solution was added. Solution was mixed well. Then 0.4ml (400µl) of sample solution under study was added and mixed well. Whole assembly was kept in ice for 15 minutes. After 15 minutes 1.5ml (1500µl) of KO_2 added. Absorbance was taken at an interval of 30 sec. Absorbance was measured at 560nm[9].

$$IC_{50}\ \text{value} = \frac{IC_{50}\ \text{of sample} - IC_{50}\ \text{of control}}{IC_{50}\ \text{of control}} \times 100$$

2.4.2 *In vitro* inhibition of DPPH Assays:

DPPH (1, 1-diphenyl-2-picryl-hydrazil) is a stable free radical. Methanolic solution of DPPH is

used to evaluate the antioxidant activity of several synthetic compounds. Antioxidant on interaction with DPPH, both transfer electron or hydrogen atom to DPPH, thus neutralizing its free radical character and convert it to1,1-diphenyl-2-picryl hydrazine. The degree of discoloration indicates the scavenging activity of the drug .The change in absorbance produced at 517 nm has been used as measure of its antioxidant activity.DPPH solution was prepared by dissolving 33 mg of DPPH in 1 lit. of methanol just before use and kept in dark amber colored bottle to protect from sunlight. Sample preparation prepared by a 1000µM/ml stock solution of ligands, metal complex and ascorbic acid had been prepared. Different concentration of ligands, metal complexes and ascorbic acid were prepared .From this stock solution 1ml has been pipette out and 5ml methanolic solution of DPPH was added, shaken well and the mixture was incubated at 37^0C for 30 min. The absorbances of all samples were measured against blank at 517 nm. The absorbance of DPPH reagent alone was taken as control. The % radical scavenging activity can be calculated following formula and calculated IC50 value[9]

$$\%\text{free radical scavenging activity} = \frac{\text{Absorbance of control - Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

3. RESULT AND DISCUSSION

Physical properties of the gtfl and coordination compounds are listed in (**Table 1)**.The result from table 1 show that the ligand coordinate to the Cu(II),Zn(II) and Vo(II) ions in 1:2 molar ration respectively. All compounds stable in air. The melting points of the complexes are higher than that of the ligand revealing that the complexes are much more stable than ligand. The products were insoluble in water, ethanol, acetone and 2-propanol.

3.1Structural Characterizations:

3.1.1Infrared Spectroscopy:

The IR spectra of the quinolone metal complexes are always found to be quite complex [10] Water molecules considerably influence the appearance of the spectra of these metal-quinolones [11].The selected frequencies observed for the metal complexes synthesized in the present work are shown in the (**Table 2)**. In the IR spectrum of (gtfl) **1** the carboxylate-stretching mode $\nu(c=o)_c$ is observed at 1728 cm^{-1}, while the pyridone carbonyl stretching frequency $\nu(c=o)_p$ is seen at 1631 cm^{-1} respectively. The former disappears on metal complexation [12]. As seen in the IR spectra of **2-4** in **Fig.2**while the latter is shifted to lower energy side indicating the involvement of the corresponding function in metal binding[13].In the complexes the disappearance of the carboxylic stretch and the simultaneous appearance of the two new bands at the region 1580-1560 and 1385-1315 cm^{-1} indicate the deprotonation of the carboxylic proton and its participation in the metal coordination as suggested by Macias *et al* [14] .Compound **3** exhibits ν (ν=o) stretching frequency in vanadium complex at 954 suggest that a mononionic ligand lies in transposition to the O_v ($o_{vanadyl}$)[15].All compounds exhibit a broad band around 3500-3380 cm^{-1} that is indicative of the presence of lattice water molecules [16]

3.1.2 Electronic Spectroscopy:

The electronic spectra of the synthesized compounds were recorded in DMSO solvent and are summarized in Table 3.2 along with their probable assignments. Two intense bands are seen around 300 nm, another around 380 nm, while a broad band centered at around 690-710 nm is assigned to metal based d-d transition observed in most of the square pyramidal Cu (II) and Vo(II) complexes[17]. The intense absorptions in the range 260-280 nm and 300-400nm correspond to$\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions respectively. The absorption around 400 nm can be assigned to the metal to ligand charge transfer band (MLCT). Mendoza-Diaz et al have noted similar observations in case of the square-pyramidal complexes of Cinoxacin and Nalidixic acid [18].In the visible region compounds show in **Fig.3** one broad band centered in the region 640-800 nm respectively, which can be assigned to $^3B_{1g}\rightarrow{}^2E_{2g}$transition in the $D4^{th}$ symmetry [19] The electronic spectra of the synthesized compounds as in (**Table 3)** show d-d transitions in the region which are typical of the five-coordinated square-pyramidal copper (II) complexes which tend to have an absorption at slightly higher energy than the corresponding six-coordinate octahedral compounds [20] .In zinc complex not observed d-d transition due to absence unpaired electron in d-orbit.

3.1.3Magnetism and Electron Paramagnetic Resonance:

Magnetic moments for the synthesized complexes were calculated at room temperature from the molar magnetic susceptibilities using Pascal's constants and the values are listed in (**Table 4)** The lowered magnetic moment of 1.56 BM observed for 2 arises out of the weak antiferromagnetic exchanges within the dimeric unit at room temperature. The room temperature magnetic moments of the synthesized metal ligand complexes 2 and 3 are round to fall in the range 1.75 -1.87 B.M indicating them to be monomeric compounds. The EPR spectrum of the metal conjugates 2 and 3 were measured in DMSO glass at 100K which yielded g_{ll} and $g_{\perp}$ values corroborating the square pyramidal geometry for the copper center [21] as seen in **Fig.4** The existence of $g_{\perp}$ value lower than the g_{ll} value ($g_{ll} > g_{\perp} > 2.0023$) indicates that the unpaired electron most likely resides in the d_{x2-y2} orbital having $^2B_{1g}$ as the ground state [22] The geometric parameter G which is a measure of the exchange interaction between copper

centers in the polycrystalline compound, is defined as $G = [g_{//} - 2.0023]/ [g_{\perp} - 2.0023]$

Here the value of G is found to be greater than 4, which is indicative of that there are no magnetic exchange interactions between the copper centers of these compounds in DMSO solvent [23]. The EPR spectrum of VO $(gtfl)_2$ exhibits characteristic signal for mononuclear VO complex. We have estimated the parameter $g_{//}$ and $A_{//}$ by considering the position of outer most line. We found that $g_{//}$ = 1.95 and $A_{//}$ =180.These values support an O_4 basal plane of the octahedron. Kivelson and Neiman have shown that $g_{//}$ is a moderately sensitive function for indicating covalent or ionic interaction. The small $g_{//}$ values (< 2.3) indicate strong interaction between the ligand and the Cu (II) ion that in turn reveals the covalent character of the bonding while compounds having the $g_{//} \geq 2.3$ have been shown to possess ionic character for the metal-ligand bond. In the present study, the $g_{//}$ value is slightly higher than 2.3 for copper complex 2 suggesting the presence of a small amount of ionic character of the metal-ligand bond. Vanadium complex show covalent character. Zinc complex not show EPR spectrum due to absence unpaired electron in d-orbit.

3.1.4 1H NMR Spectroscopy:

^{1}H NMR spectra of copper complex of gtfl **(2)** shown in **Fig.5,** which were carried in DMSO-d6 as solvent. In copper complex, coordination of copper through the carboxylic group (the hydrogen signal of (COOH) is absent and the peak at δ 3.55 ppm was assigned to water molecules within the complex, which was not detected in the spectra of free gtfl ligand.There is an increasing and decreasing in the chemical shift of protons of piperazine and aromatic ring compared with the ligand .This shift is due to the complexation and differences in the configuration of complex than ligand.Summarizes the ^{1}H NMR spectral data of free gtfl ligand and Cu $(gtfl)_2(H_20)_2$ compound shown in (**Table 5).**

3.2 *In Vitro* Antioxidant Activity

3.2.1Super oxide dismutase activity

The anticancer activity of copper conjugates has been shown to be related to their antioxidant properties and hence synthesized compound were evaluated for their superoxide dismutase activity using the NBT assay. The enzyme that helps control production of radicals is superoxide dismutase (SOD).Many human tumors have been shown to express high level of SODs, which has been associated with aggressive tumor characteristic. Thus, it can be anticipated that compounds having good SOD activity generally posses excellent antitumor activity[24].

SOD activity is frequently assayed with indirect assay that involves the addition of superoxide generator and a detector whose reaction with superoxide is spectrophotometrically monitored. The presences of SOD in a sample inhibit the reaction between superoxide and the detector by competing for the superoxide supplied by generator. The degree of inhibition is proportional to the activity of SOD in the sample. Several super oxide generator and detector have been used in combination to assess in vitro SOD activity. The SOD activity has been expressed in terms of IC50 values, implying inhibition of superoxide radical at 50% concentration. The lower the IC50 value, the higher is the potency of the compound in dismuting the free radical. In the metal complexes, zinc-gatifloxacin (4) is found to be most potent compound with IC_{50} of 4 **(Fig. 6)**. While the order of activities for metal complexes are in the order **4 > 3 > 2**.

3.2.2 DPPH activity:

DPPH(1,1-diphenyl-2-picryl hydrazyl)**(1**)is characterized as a stable free radical by virtue of the delocalization of the unpaired electron over the molecule as whole, so that the molecules do not dimerise, as would be the case with most other free radical. The delocalization also gives rise the deep violet colour, characterized by an absorption band in ethanol solution, centered at about 520nm.When a solution of DPPH is mixed with that of a substance that can donate a hydrogen atom, then this gives rise to the reduced form (**2**) Shown in **(Fig. 7)** with the loss of this violet colour. In the present case, zinc-gatifloxacin 4 complex was found to be most potent compound with IC_{50} value of 3.5 **(Fig. 8)**.

Table 1 Physical properties of gatifloxacin and their metal complexes.

Comp.	Molecular Formula	Molecular Weight	Colour	Yield (%)	M.P (^{0}c)
1	$C_{19}H_{22}FN_3O_4$	375	White	---	185
2	$Cu(C_{38}H_{48}F_2N_6O_6)$	849	Green	85	265
3	$VO(C_{38}H_{44}F_2N_6O_4)$	880	Light Green	85	245
4	$Zn(C_{38}H_{44}F_2N_6O_4)$	879	White	80	251

Table 2: IR frequencies values of Gatifloxacin and their metal complexes.

Comp	ν(O-H)	$\nu(C=O)_c$	$\nu(C=O)_p$	$\nu_{asym}(COO)$	$\nu_{sym}(COO)$	ν (M=O)
1	3415	1728	1631	-----	**----**	**----**
2	3410	----	1618	1574	1383	----
3	3434	----	1623	1578	1385	954
4	3420	----	1629	1580	1380	----

All values in cm^{-1}, c=carboxylic acid, p=pyridine, sym=symmetric and asym = asymmetric

M= metal

Table 3: Absorption bands in UV of Gatifloxacin and their metal complexes.

Comp.	Intraligand	MLCT	d-d
1	284	----	---
2	298	360	717
3	300	360	701
4	298	360	---

All the values in *nm.*

Table 4: Magnetism and Electron paramagnetic resonance spectra of metal complexes of gatifloxacin.

Comp.	μ_{eff} (BM)	g_{ll}	$g_{\perp}$	A_{ll} (10^{-4}) (cm)	f (cm)
2	1.77	2.31	2.06	167	138
3	1.82	2.00	1.97	180	109

Table 5:[1]H NMR spectral data of gtfl and Cu $(gtfl)_2(H_20)_2$ compound

Gtfl	**$Cu(gtfl)_2(H_20)_2$**	**Assignments**
1.10	1. 13	$\delta H,-CH_3$
6.68	6.06	δH,-CH (*Aromatic)*
1.35	1.35	δH,-CH (*Cyclopropane*)
11.0	….	δH,-COOH
….	3.55	$\delta H,H_2O$

All the values in *ppm*

Figure 1: Structure of Gatifloxacin

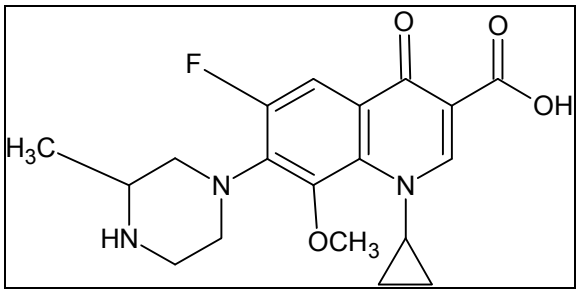


Figure 2: Infrared spectra of gatifloxacin (1) and their metal complexes (2-4).

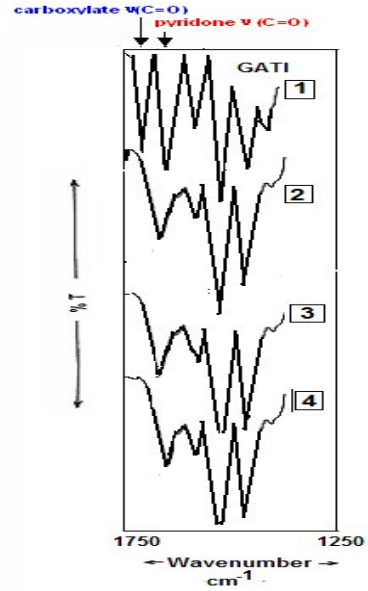


Figure 3 Electronic spectra of gatifloxacin and its metal complexes

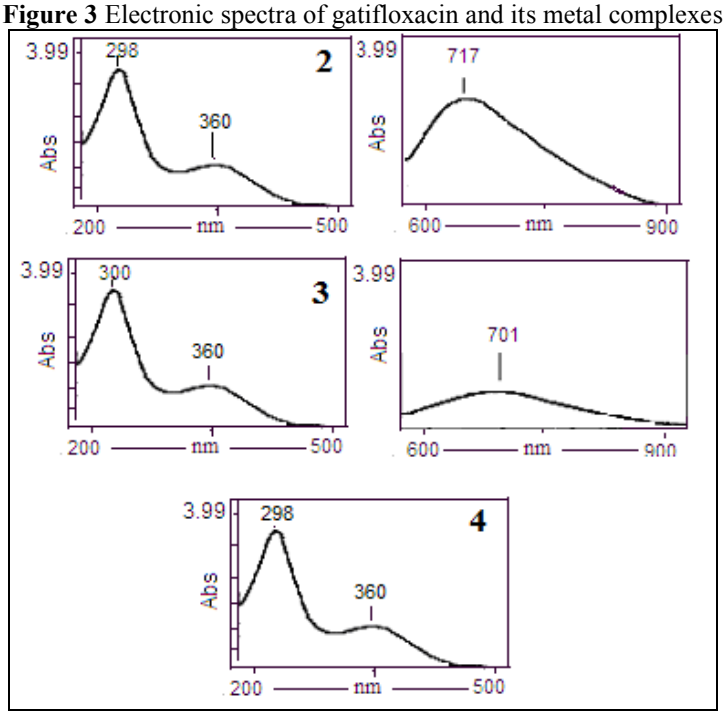


Figure 4: EPR spectra of copper and vanadium complexes of Gatifloxacin

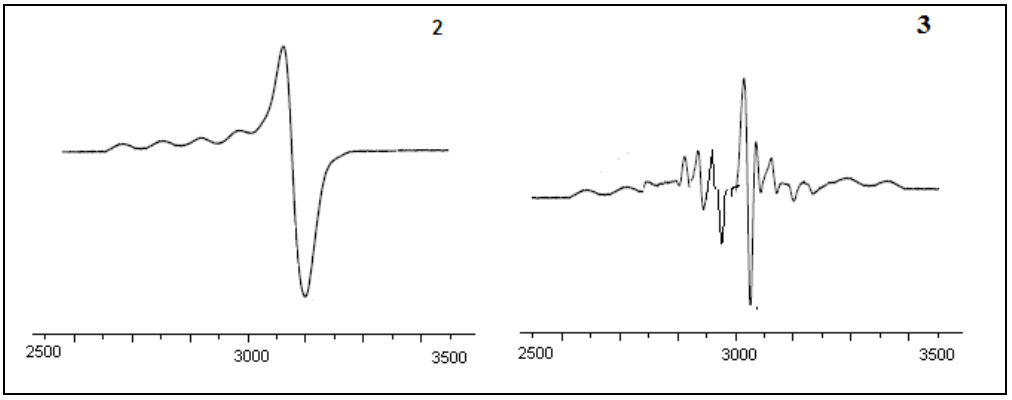


Figure 5: ^{1}H NMR spectra of copper complex of Gatifloxacin

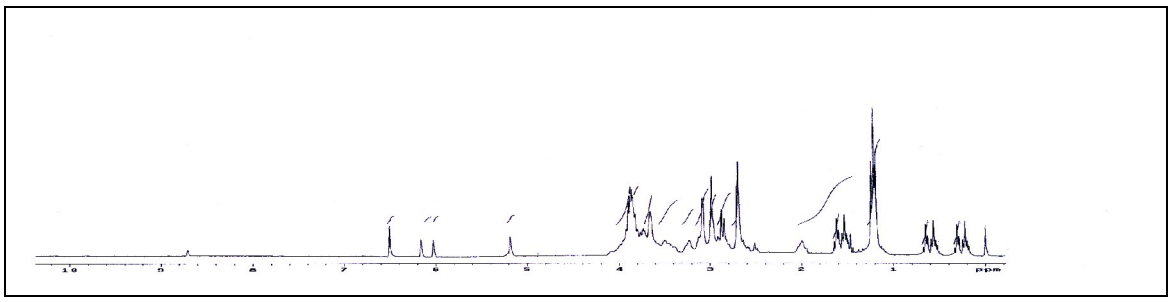


Figure 6: IC_{50} values of metal complexes of gatifloxacin using SOD assay

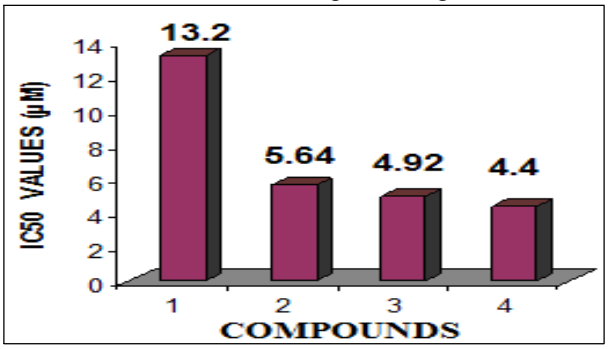


Figure 7: Reaction mechanism of DPPH free radical scavenging assay.

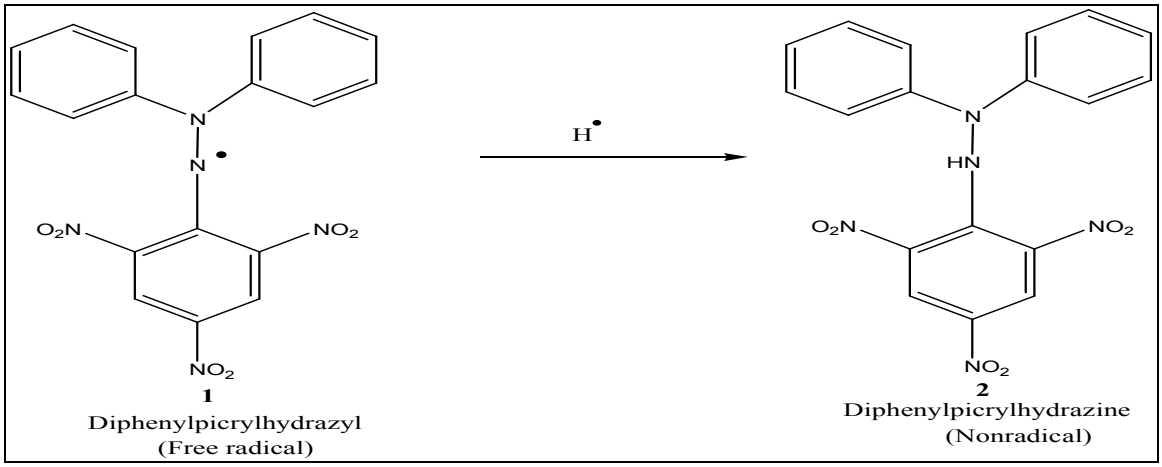
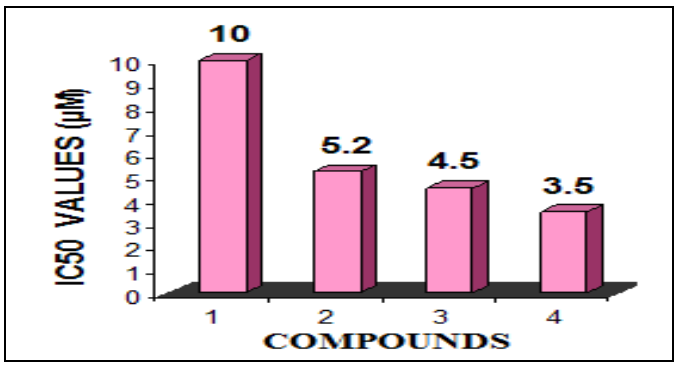


Figure 8: IC_{50} values of metal complexes of gatifloxacin using DPPH assay



CONCLUSION

The synthesis and characterization of three mononuclear complexes of the gatifloxacin with Cu, VO and Zn has been realized with physiochemical and spectroscopic methods and anti-oxidant activity. In all complexes gatifloxacin bound to the metal via pyridone and one carboxylate oxygen atoms. The metal complexes revealed high DPPH scavenging and potent SOD mimics activity in comparison to the free gatifloxacin. As a result, this study provides evidence that the chelation of different metal complexes with gatifloxacin had significant influence on the antioxidant activities in different in vitro model system. However, its antioxidant activity can be further confirmed by *in vivo* methods.

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