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SYNTHESIS AND CHARACTERISATION OF MIXED LIGAND METAL COMPLEXES OF MEFLOQUINE AND CHLOROQUINE

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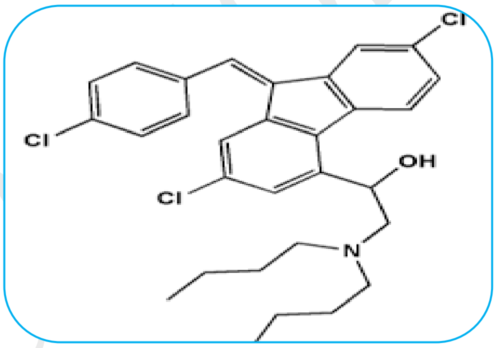
ABSTRACT:
The basic aim of the study is to find molecules that can be more effective therapeutic substitutes from the available antimalarial drugs.Efforts have also been made on combination of antimalarial drugs for effective control of a large number of diseases. The combination of two short half-life drugs, namely Artesunate and Lapdap (Proguanil and Dapsone) has proved the benefits of combination therapy in rapid removal of of parasites from the blood stream.



KEYWORDS: *basic aim , benefits of combination therapy.*

INTRODUCTION

The resistance of these parasites to antimalarial drugs has made an effort to reexamine the pharmacology of alternative antimalarials, which may be effective against resistance strains. The introduction of fluorine can have a prolonged effect on the biological activity and the physico-chemical properties of the aromatic compounds. Niel*et al*. reported that the presence of fluorine in the aromatic nucleus of amodiaquineand substitution at the 2, 6 position and replacement of the 4-hydroxyl group of the amodiaquine produced analogue drugs that maintain antimalarial efficacy in vitro and are more resistant to oxidation. Since the two ligands in this study (mefloquine and chloroquine) possess active binding sites, it was decided to study their coordination tendencies, characterisation after complexing with metals and their biological activities.[1.2]

SYNTHESIS OF THE METAL COMPLEXES

Ethanolic solutions of the metal chlorides were prepared in round bottom flasks. 0.01Mol (4.148 g) of mefloquine was mixed with 0.01 mol (4.179 g) of chloroquine in a beaker. The mixed ligands were dissolved in 20 ml of ethanol and added to the solution of the corresponding metal salt dissolved previously in 10 ml of ethanol at a pH of 8.5.The solution was refluxed for 2 h. The metal chelates crystallized, after leaving the reacting solution for about 30 minutes in a refrigerator. The metal complexes thus separated were filtered and washed with ethanol and then with distilled water to remove unreactedligand and metal, finally the solid complexes were dried in a desiccator. On the basis of elemental analysis the metalcomplexeswereformulated as$[Cu(cq)(mq)Cl_2].2H_2O$,$[Zn(cq)(mq)Cl_2].2H_2O$,$[Ni(cq)(mq)Cl_2].6H_2O$,and $[Fe(cq)(mq)(H_2O)Cl_3].5H_2O$

RESULTS AND DISCUSSION

ELEMENTAL ANALYSIS

Elemental analysis (Table.1) shows that the ligands (mefloquine and chloroquine) and the metal salts are in the ratio of 1:1:1.

IR spectra

The IR spectra of the ligand shows the stretching frequencies at 3200cm^{-1},1080cm^{-1}, 3200 cm^{-1}, 1200cm^{-1}and 650cm^{-1} due to -NH, CN, -OH group, C-F bond and C-Cl bond, respectively.During complexation (Fig 2),the stretching frequency of NH group gets shifted to 3250cm^{-1}indicating the involvement of NH group in metal coordination.The presence of coordinated water in Fe(III) was confirmed by the medium strength bands at 840–850 cm^{-1}characteristic of $\upsilon(H_2O)$ frequencies.These bands were not observed in the spectra of other metal complexes indicating the absence of coordinated water molecules.The vibrational status of those ligands upon complexation to the metal ion is indicated by the shift in frequencies of the bands of the complexes compared to those of the ligands.[3]

Electronic spectra

There are two absorption bands, assigned to n–π* andπ–π* transitions, in the electronic spectrum of the ligand.These transitions are also found in the spectra of the complexes (Fig 3)but they are shifted towards lower and higher frequencies, confirming the coordination of the ligand to the metallic ions.The electronic spectrum of copper(II) complexexhibits bands at 467 nm and 645nm which are assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_1g \rightarrow {}^2E_1g$ transitions [4]. These transitions and the measured value of the magnetic moment (μ_{eff} = 1.88 BM) suggest a square-planar geometry of the complex. Since the zinc ion has d^{10} configuration, the absorption at 371nm could be assigned to a charge transfer transition.On the basis of spectral data and the configuration of the zinc(II) ion, a tetrahedral geometry could be assumed for its complex. The Ni(II) complexshows a magnetic moment of 3.26 B.M. The electronic spectrum oftheNi(II)complex shows a band at 832-816nm which corresponds to the transition $^3T_1(F) \rightarrow {}^3T_1(P)$ in tetrahedral environment.The magnetic moment for high spin octahedral Fe(III) ion ranges from 5.7 to 6.0 BM. The observed magnetic moment value is well within the accepted range and hence an octahedralgeometry is proposed for the Fe(III) complex.

ESR spectrum

In square-planar complexes(Fig 4) the unpaired electrons lie in the $d_{x^2-y^2}$ orbital giving $^2B_{1g}$ as the ground state with $g_{||} > g_{\perp}$while the unpaired electron lies in the d_{z^2} orbital giving ^2A_1g as the ground state with $g_{\perp} > g_{||}$. From the observed values, it is clear that $g_{||} > g_{\perp}$, which indicates that the structure of the complex is square-planar and that the unpaired electron is predominantly in the $d_{x^2-y^2}$ orbital .

^{1}H NMR spectrum

The signal at δ 3.6 (s, 1H) is assigned to hydroxyl proton (OH) and the signal at δ 2.0 (s, 1H) is assigned to piperidine proton (-NH) in mefloquineligand. The signals due to (-NH) are shifted to downfield in the spectrum of the zinc complex indicating the coordination of –NH group with metal ions (Fig.5). The signal due to aromatic protons at δ6.94 – 7.83 shifted downfieldin the complex. In the same way –NH proton appearsat δ4.0, CH protons of quinoline appears at δ8.36, CH_2 protons appears at δ1.37,and CH_3 protons at δ1.02in the chloroquineligand shifted to downfield in the zinc complexes.Thus^{1}HNMR observations are supplemented with the assigned geometry.[5]

TGA study

TGA study ofCu(II)complex (Fig.6)indicates that it undergoes three stages of decomposition. The complex starts to decompose above 50°C. The initial decomposition temperature was observed at 253.4°C corresponding to 10% weight loss. The second stage of decomposition occurs at ~ 340°C, bringing ~ 19% weight loss. 50% weight loss occurs at 660°C. 90% decomposition takesplace at 900°C.The residual weight at 700°C for the Cu(II)complex (47.78%) corresponds to the amount of copper oxide formed at the temperature[6,7].

DSC studies

The DSC studies of nickel complex (Fig .7)indicate that it shows the glass transition temperature at 185.1°C. The endothermic peaks observed at276.3°C and 340°C can be due to decomposition and melting of the complex [8.9].

XRD studies

The XRD pattern of the Cu(II) , Ni(II), Fe (III) and Zn(II) complexes (Fig.8) were recorded in the 2θ range 20-80°. The crystalline size of the copper complex calculated from Scherer's formula was found to be 46nm indicating its nanocrystalline nature.[10]

SEM studies

SEM study of Ni(II)complex (Fig .9) indicates the presence of well defined crystals free from any shadow of the metal ion on their external surface.[11]

FAB mass spectrum

The FAB mass spectrum of the mixed ligand copper complex (Fig10)of mefloquineand chloroquineshows the molecular peaks at m/z 868 which confirms the stoichiometry of the metal complexes. Other fragments obtained are $(C_9H_5NCl)^+$, $(C_9H_{19}N)^+$, and $(C_{17}H_{15}OF_6)^+$ and their molecular ion peaks are observed at m/z 162, 141, and 343 respectively.[12]

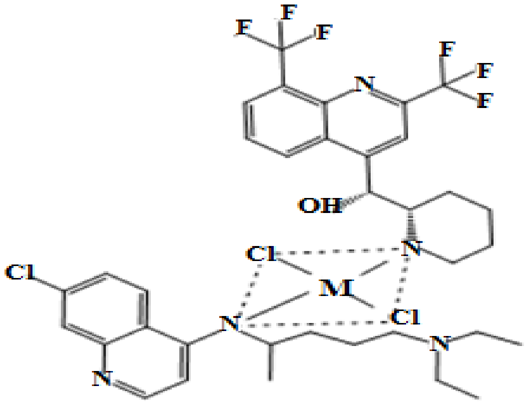
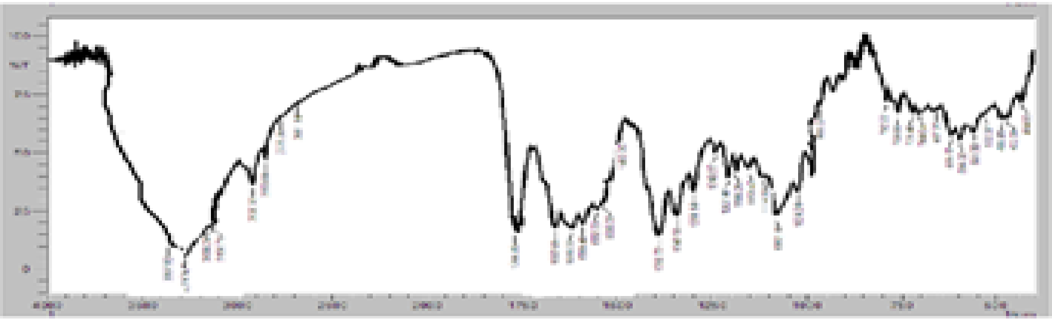


Fig 1 Geometry of mixed ligand metal complex of chloroquine and mefloquine
M = Cu(II)

Table. 1 Elemental analysis of mixed ligand metal complexes ofchloroquine and mefloquine

Compound	C%(found)	H%(found)	N%(found)	Metal%(found)
$[Cu(cq)(mq)Cl_2]. 2H_2O$	48.37(48.27)	5.34(5.36)	8.06(8.16)	7.32(7.26)
$[Zn(cq)(mq)Cl_2] .2H_2O$	48.27(48.31)	5.33(5.32)	8.05(8.12)	7.52(7.63)
$[Fe(cq)(mq)(H_2O)Cl_3] .5H_2O$	43.59(42.99)	5.62(5.59)	7.23(7.17)	5.77(5.79)
$[Ni(cq)(mq)Cl_2] .6H_2O$	44.9(43.77)	5.82(5.79)	7.48(7.39)	6.27(6.19)



Wave number(cm^{-1})

Fig 2 IR spectrum of [Fe(cq)(mq)(H_2O)Cl_3].5H_2O

Table 2 IR spectral data of mixed ligand complexes of chloroquineand mefloquine

Compound	**υ(NH)**	**υ(CN)**	**υ(OH)**	**υ(C-Cl)**	$\upsilon_{(H2O)}$
Ligand	3200	1080	-	-	
[Cu(cq)(mq)Cl_2]. 2H_2O	3100	1010	3100	650	-
[Zn(cq)(mq)Cl_2] .2H_2O	3150	1020	3120	640	-
[Fe(cq)(mq)(H_2O)Cl_3] .5H_2O	3120	1030	3130	630	840
[Ni(cq)(mq)Cl_2] .6H_2O	3220	1020	3110	635	-

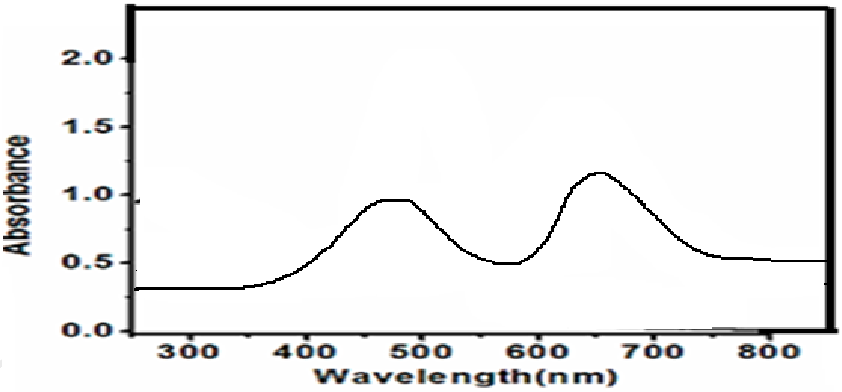


Fig .3 Electronic spectrum of [Cu(cq)(mq)Cl_2].2H_2O

Table .3Electronic spectraldata of mixed ligand complexes of chloroquine and mefloquine

Compound	**Transition**	**Wavelength(nm)**	**Geometry**	μ_{eff}
Ligand	π→π* and n→π*	Below 250	-	-
[Cu(cq)(mq)Cl_2]. 2H_2O	$^{2}B_{1}g\rightarrow{}^{2}E_{1}g$	467,645	Square planar	1.88
[Zn(cq)(mq)Cl_2] .2H_2O	-	-	tetrahedral	diamagnetic
[Fe(cq)(mq)(H_2O)Cl_3] .5H_2O	$^{6}A_{1}g\rightarrow{}^{4}T_{2}g$(G)	477-498	Octahedral	5.7-6.0
[Ni(cq)(mq)Cl_2] .6H_2O	$^{3}T_{1}$(F)$\rightarrow{}^{3}T_{1}$(P)	832-816	tetrahedral	3.26

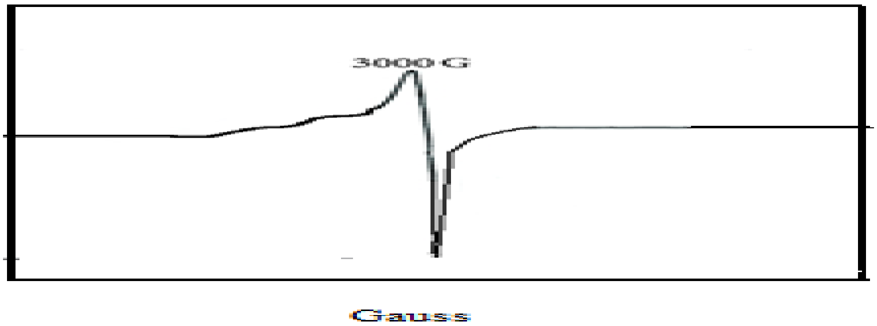


Fig .4 ESR spectrumof $[Cu(cq)(mq)Cl_2].2H_2O$ at 300K

Table 4 ESR spectral data of $[Cu(cq)(mq)Cl_2].2H_2O$

Complex	$g_{\|}$	$g_{\perp}$	g_{iso}	$K_{\|}$	$K_{\perp}$	α^2	β^2	γ^2	G
$[Cu(cq)(mq)Cl_2]$ $2H_2O$ 77K	2.212	2.202	-	0.78	0.526	1.246	0.7351	0.775	7.4
$[Cu(cq)(mq)Cl_2]$ $2H_2O$ 300K	-	-	2.10	-	-	-	-	-	-

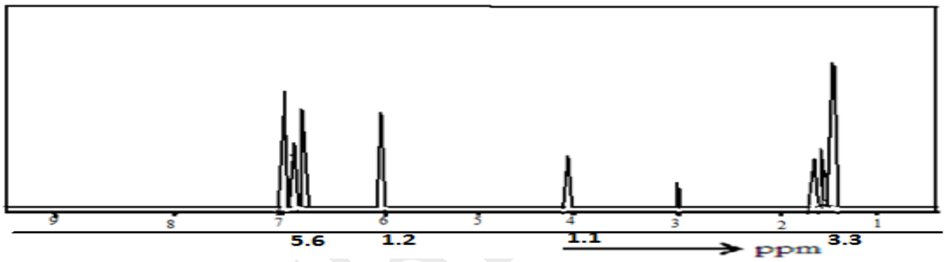


Fig .5^{1}H NMR spectrum of $[Zn(cq)(mq)Cl_2].2H_2O$

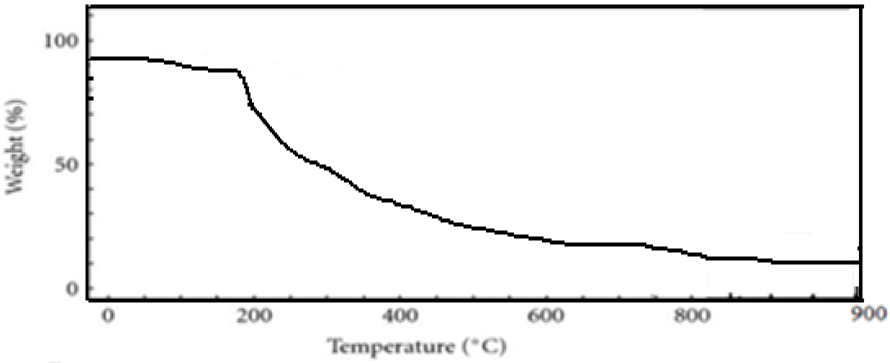


Fig .6TGA patternof $[Cu(cq)(mq)Cl_2].2H_2O$

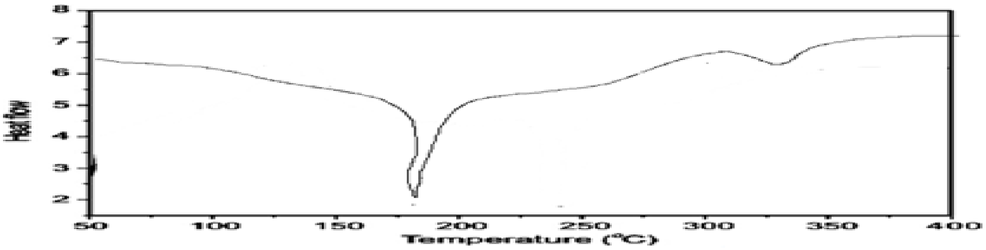


Fig.7 DSC pattern of$[Ni(cq)(mq)Cl_2].6H_2O$

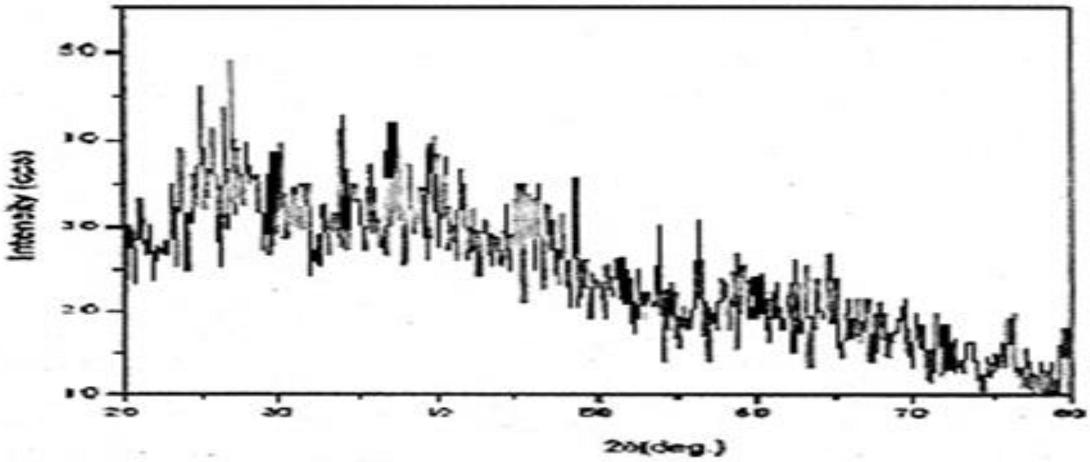


Fig 8Powder XRD pattern of $[Cu(cq)(mq)Cl_2].2H_2O$

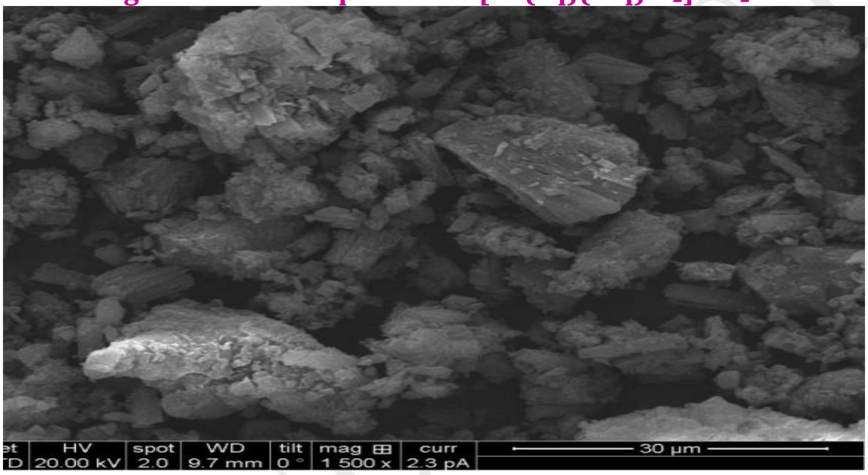


Fig 9 SEM image of$[Ni(cq)(mq)Cl_2].6H_2O$

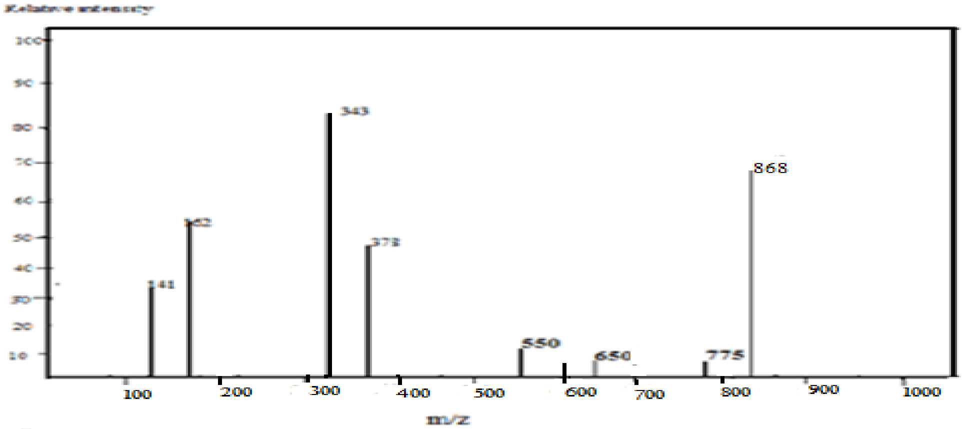


Fig.10 FABMass spectrum of $[Cu(cq)(mq)Cl_2].2H_2O$

[1] Gielen M.,Tiekin R.T.,Metallotherapeutic Drugsand Metal-BasedDiagnostic Agents, the Use of Metals in Medicine, Wiley,Chichester,2005.

[2] WederJ.E., DillonC.T., Hambley T.W.,KennedyB.J.,Lay P.A.,BiffinJ.R., Regtop., Daview H.L.,Copper complexesofnon-steroidalanti-inflammatory drugs,*Coordination Chemistry Reviews*, 2002, 232(1-2),95-126.

[3]GallardoJorgeL.,Colin Miguel C., *Surface Spectrscopy for Engineers and Scientists*, Create Space Independent 2013. ISBN 978-1483999968.

[4] Figgis B.N., Introduction to Ligand Fields, Interscience Publishers, 1967, 285.
[5] Nagajothi A., Kiruthika A., Chitra S.Fe(III) Complexes with Schiff base, Synthesis, Characterization, Antmicrobial studies Research Journal of Chemical Sciences
2013,3(2),35-43.
[6] DeaconG.B.,PhillipsA.D., Relationships between the carbon-oxygen stretching frequencies of carboxylato complexes and the type of carboxylate coordination. *Coordination Chemistry Reviews*,1980,33(3),227–250.
[7] El-WahedM.G.A.,Refat M.S,El-Megharbel S.M., Synthesis,spectroscopicand thermal characterization of some transition metal complexes of folic acid. *SpectrochimicaActa* , 2008,70(4),911–916.
[8] Holde V.K.E., JohnsonC.W., Ho S.P.,Thermodynamics and biochemistry. In Principles of Physical Biochemistry, 2006,72–105.
[9] CooperA.,NutleyM.A.,Walood A.,Differential scanning microcalorimetry. Protein-Ligand Interactions: Hydrodynamics and Calorimetry, 2000, 287–318.
[10] EfthimiadouE.K., SanakisY.,RaptopoulouC.P.,Karaliota A.,KatsarosN., PsomasG.,Crystal structure, spectroscopic,andbiological study of the copper(II) complex with third-generationquinolone antibiotic sparfloxacin,*Bioorganic and Medicinal Chemistry Letters,* 2006,16(14), 3864–3867.
[11] LeeJ.D,*Concise Inorganic Chemistry,Blackwell Science*,1996,35,196—231,663-671.