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A Review of Antifungal Activities of Various Flouroquinolone and Its Metal Complexes

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ABSTRACT

Superficial fungal infections are common worldwide.Fungal infections are a growing challenge in immunocompromised patients. The prolonged use of traditional antifungals to treat fungal infection has caused the emergence of drug resistance, Therefore, demand of new therapeutic strategies for fungal infections are warranted. Quinolones and Flouroquinolones displayed potential anti-fungal activity and some of them could significantly increase the susceptibility of antifungals.Metal complexes of Flouroquinolones with specified antimicrobial activities, are a new entry in the field of bioinorganic. Antifungal activities of few metal complexes of Flouroquinolones arereviewed in this paper by comparing the zone of inhibition values.Some of them found to exhibit excellent potency against both drug- susceptible and drug- resistant fungi where as some found to show lesser or no antifungal behaviour as compared to the parent drug.The objective of this review is to contour the recent advances in flouroquinolone derivatives as promising antifungal agents and summarize the coordination behaviour of the drug with metal ions to provide cognizance for the design of more active candidates.

Key words: Immunocompromised, Antifungal behaviour, Flouroquinolones, Metal complexes

1. INTRODUCTION

Around 50 fungal species are known to cause human illnesses, and in excess of 300 million individuals experience the ill effects of the occurrence of life- threatening Invasive Fungal Infections (IFIs), leading to over 1.35 million deaths every year, all over the world. Moreover, the mortality is further aggravated by the rapid development of resistance against the existing antifungal drugs. *Candida albicans, Crypto coccusneoformans, and Aspergillusfumigatus* are the most well-known types of Fungus liable for IFIs. At present, the antifungal species accessible for clinical purpose are fairly restricted, and practically none of them are ideal as far as viability, antifungal range or safety measures are concerned[1-3]. Quinolones are broad-spectrum antibiotics with excellent capability of oral absorption and good bioavailability. However, it's several derivatives having different atom at various position of the ring structure imparts various desirable properties to the quinolones, Flouroquinolones(FQ) are included in this category.Flouroquinolones have remarkable property to form metal complexes like the quinolones. The interaction between FQ and metal ions was suggested through chelation between the metal and the carbonyl and carboxyl groups of FQ. Flouroquinolones can bind to several divalent and trivalent metal ions,such as Mg^{2+}, Cd^{2+}, Ca^{2+}, Mn^{2+}, Ni^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+}, $Fe^{2+/3}$ and Al^{3+}, and may result in aleration of their activity.[4-6] The area of bioinorganic science, which manages the investigation of role of metal complexes in biological frameworks, has opened another perspective for scientific research toward this path. It has been demonstrated that introduction of metals into Flouroquinolones could profoundly affect biological systems. Some derivatives of metals, for example, ferrocene were utilized to improve the antiplasmodial action of fluoroquinolone like ciprofloxacin, or to make novel dual- action hybrids with profoundly encouraging outcomes. Additionally, on-going investigations recommended that the joining of metals into the fluoroquinolones is a fundamental advancement in the activity of these drugs[7-9]. The pharmacological behaviour of these metal complexes profoundly reliant on the nature of metal cation, its ligands and the structure of the complex. Number of studies confirmed that various drugs possess mutated pharmacological and toxicological properties in their metal complexes.Investigations and research has revealed that these metal complexes exhibit an admirable antibacterial or anticancer activity as compared to the free antibiotic[10-15]. Antifungal behaviour of the

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flouroquinolone metal complexes is not much explored as the parent drug itself shows lesser fungicidal activity. In this review paper we have reviewed the Antifungal activity of few flouroquinolones- Gatifloxacin(GATI), Gemifloxacin(GEMI), Ofloxacin(OFLX), Norfloxacin(NFLX), Levofloxacin(LEVO), Lomefloxacin(LOME) and Sparfloxacin(SPAR). The fungicidal behaviour of metal complexes of these flouroquinolones with various metal ions is compared with the respective parent drug.

2. FLOUROQUINOLONES AND ITS METAL CHELATES:

Flouroquinolones are modified quinolones in which a Flourine atom is introduced at position 6 in ring structure. This new subclass of quinolones shows better potency andbroad spectrum antibiotic properties. The basic chemical structure of all Flouroquinolones includes- a carboxylic acid group at the 3-position, a carbonyl oxygen atom at the 4-position and in most cases a basic piperazinyl ring (or another N-heterocycle) at the 7-position.(**Fig 1**), so they can act as bidendate, unidentate and bridging ligand which is the basis of their extraordinary capacity to bind metal ion. The moiety present at N-1 and at C-7 position have a strong impact on the microbiological activity and the pharmacokinetic properties of drugs. In addition to that, presence of fluorine atom at position 6 and the piperazine ring or methyl piperazinyl group at position 7 characterise their structure and appreciably upgraded the spectrum of their activity.The mode of action adopted by fluoroquinolonesincludes interactions with two peculiar enzymes of DNA synthesis- topoisomerase IV and topoisomerase II. These interactions are recognized as drug targets. Inhibition of DNA synthesis by fluoroquinolones requires the targeted topoisomerase to possess DNA cleavage capability. Due to this specific mode of action, they are considered to be the broadspectrum antibiotics active against various microbes.

Flouroquinolones possess incredible tendency to bind to several divalent or trivalent metal ions,such as Mg^{2+}, Cd^{2+}, Ca^{2+}, Mn^{2+}, Ni^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+}, $Fe^{2+/3}$ and Al^{3+}, and may result in alteration of their activity.In most of the flouroquinolones-metal complexes, the linkage of ligand and metal ion is through oxygen atom present in carboxylic group and carbonylgroup and thus ligand behave as bidentate O-donor by joining through two binding sites to the metal ion. FQ ligand can also be coordinated to the metal via the pyridine oxygen and one carboxylato oxygen atom.Most commonly, when the flouroquinolones behave as bidendentate ligand, they are chelated from one oxygen atoms of carboxyl anion and the other oxygen of ring carbonyl group **(Fig2)**. However, less common possibility of their chelation as bidentate ligand is when FQs coordinated either with both the carboxylic oxygen atoms(**Fig 3**) or with both piperazinic nitrogen atoms(**Fig 4**). Flouroquinolones can also act as unidentate ligand by binding through terminal piperazinylnitrogen(**Fig 5**). Hence, it is observed that flouroquinolones do not possessany single mode of metal complexation. Ligand can bind with divalent ions in 1:1 or 1:2 ratio (metal:ligand) and with trivalent ions, in 1:1 or 1:3 ratio, rarely 1:2.The formation of FQs-metal complexes generally alters the biological properties of the parent compound.The interactions of metal ions with fluoroquinolones are indispensable for the antimicrobial behaviour of these drugs, as the metal ions may bridge the binding of the drug to DNA gyrase(topoisomerase II) or of microbial DNA directly.Many FQ-metal complexes are found to show not only antibacterial but also good antifungal activities.

3. ANTIFUNGAL ACTIVITES OF FLOUROQUINOLONES:

Periphral fungal infections are customary throughout the world. These infections occur in both healthy and immunocompromised patients. They are believed to affect 20–25% of the world's population, and the incidence continues to increase[18,19]. For over two hundred years quinolone entity has been utilized as a platform for medicine advancement and even in present era, it act as a limitless motivation for design and development of novel man-made agents showing broad spectrum behaviour. Besides classic antibacterial activity, fluoroquinolones also possess various atypical biological prosperities, such as antifungal, antiparasitic, antiviralactivity.The increasing administration of antifungal agents to treat fungal infections has led to the development of fungal resistance. The emergence of resistance shows the necessity of discovering

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new antifungal agents with broader antifungal spectra, low toxicity and higher therapeutic indexes[21,22].The antifungal activities of the fluoroquinolones tested are likely to be mediated by Topoisomerase II enzyme.Belmont *et al*[22]explainedMg^{2+} modulated DNA- affinity of the fluoroquinolone, as Mg^{2+} ion plays an important role in poisoning the cleavable gyrase- DNA complex, and consequently, in eliciting antifungal activity by this family of drugs. Thus, intercalation of metals into 4- quinolones may provide more effective candidates. Sengul*et al*[23] has showed thatmoxifloxacin and gatifloxacin, drugs undiluted inhibited greater than 95% of growth of *Candida sps* in 24 hrs.Gatifloxacin and sparfloxacin showed activity in a qualitative paper disk diffusion test against *Trichophytonrubrum, Fusariumsolani,* and *Candida albicans*, but not against *Saccharomyces cerevisiae*.Dideme*t al*[24] explained that Ofloxacin, levofloxacin, fluconazole,are used as the control agents and showed strong antifungal activities against isolated strains of *Candidaalbicans*, and *Candidakrusei.*Ciprofloxacin, moxifloxacin, levofloxacin, Trovafloxacin, and Sitafloxacin enhanced the activities of antifungal agents against *Candida albicans and Aspergillusfumigatus*The in-vitro antimicrobial activities of flouroquinolone derivative against eight bacterial strains and four fungal strains (*Aspergillusniger*, *Candida albicans, Aspergillusfumigatus, and Aspergillusclavatus*) were evaluated by Patel *et al*.[25,26.] All derivatives showed weak- to- moderate antifungal activities with minimum inhibitory concentration (MIC) values in a range of 6.25– 100 μg/ml against the tested four fungi. Recently, attention has been paid to the anti-fungal activity of antibiotics and their derivatives. Studies revealed that a series of antibiotics and its derivatives obtained by inculcating metal ions into its structure, displayed potential anti-fungal activity and some of them could significantly increase the susceptibility of antifungals.

4. ANTIFUNGAL ACTIVITIES OF FQ-METAL COMPLEXES:

Although flouroquinolones themselves exhibit weak antifungal activity, some of the metal complexes generated by newer fluoroquinolones, have shownbetter activity than the parent drug.The effect of formation of metal complex on the antimicrobial behaviour of quinolones was explained first of all by Lecomte*et al* [27]and Alkaysi*et al*[28]as a negative phenomenon, and some results of decrease in the biological activity of quinolones due to the presence of metal ion, further toughen this assumption. Many research papers explainedmetal complexes of Ciprofloxacin showing lesser antimicrobial activity than the parent drug.[54-58]Whereas Moxifloxain metal complexes are found to show extraordinarily high antimicrobial activity as compared to the ligand[41-44]. But now the excellent antimicrobial behaviour of metal complexes of Flouroquinolones is undisputedly accepted by researchers. The chelation theory and overtone concept of cell permeability is helpful in explaining enhanced biological activity of metal chelates. In this review paper we have studied the antifungal activities of few metal complexes of Flouroquinolones. Flouroquinolones themselves possess poor antifungal properties but metal complexes of some newer fluoroquinolones exhibit satisfactory antifungal activity. Tumer*et al*[29]described that Fe (III), Cu (II), and Zn (II) Complexes of levofloxacin proved to have higher antifungal effects than the standard drug against *Candida albicans*. Kumar *et al*[30]explained that Complexes of gatifloxacin with Cu (II), Zn (II), Fe (III), in 1:2 (metal: ligand) stoichiometry displayed excellent antifungal properties against fungi *Trichophytonrubrum, Candida albicans and Fusariumsolani*. Their Research experimentation also revealed that some complexes of Sparfloxacin show antiparasitic activity against parasite *Trypanosomacruzi.* The antifungal activity of FQ-metal complexes is slighter as compared to their antibacterial behaviour for example, Norfloxacin metal complexes are found to exhibit very high antibacterial activity but showed no antifungal activity against selected fungi[45-51].At the same time Zn and Cu complexes of Gatifloxacin shows better antifungal behaviour against *Candida sps*.[52,53] However fungicidal behaviour of these complexes is comparable with the parent drug. In this review paper, the antifungal activities of various FQs and their metal complexes is studied by comparing the values of zone of inhibition in mm, which can be measured via disc diffusion method, qualitative antimicrobial susceptibility test. The value of Diameter of Zone of inhibition in mm, is collected from various research papers to compare the antifungal activities of FQs with that of respective metal complexes and the data is presented in tables.

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Table 1 reveals that Gatifloxacin-metal complexes show increased or similar Antifungal activity as compared with the respective parent drug.All the metal complexes of Gatifloxacin show excellent antifungal activity against *Trychophytonrubrum*, *Candidaalbicans*, and*Fusariumsolani* but shows no activity against *Sachromycescervisae*. Antifungal activities of Gemifloxacin-metal complexes are detected only in *Candida Albicans*(**Table 2**). In case of Ofloxacin, it show very poor activity against fungus but when it is complexed with Metronidazole along with various metal ions, it showed remarkable antifungal behaviour against *Candida Albicans*and*Trychophytonrubrum*(**Table 3**). Similarly when OFLX is complexedwithBipyridine and 1,10-Phenanthroline as coligand along with metal ions, then also it showed increased or similar antifungal activity. However, metal complexes of Norfloxacin, Levofloxacin and Ofloxacin studied against various fungi like *Aspergillusflavus*, *Aspergillusfumigatus* and *Alterariasps*, donot show any antifungal activity(**Table 4**). Antifungal activities of Lomefloxacin and its metal complexes are studied with four different fungi i.e. *Candida albicans, Aspergillusflavus, Aspergillus Niger* and*Sachromycescerevisieae***(Table 5)**. The drug along with metal ions showed some behaviour only towards *Candida albicans*. Eight binary and eight ternary metal complexes of Sparfloxacin are studied against two fungi *Candida albicans and Aspergillusflavus* with Amphotericin-B as standard. Cu(II), Co(II) and Ni(II) binary complexes exhibited exceptional antifungal activity with zone of inhibition comparable to the standard drug.(**Table 6)**. Similarly for ternary metal complexes Co(II) and Ni(II) complexes were found to have magnificient fungicidal behaviour against both the fungus where as other metal ions- Mn(II), Cr(II), Fe(II),La(II) and UO_2(II) donot show any activity against any fungus.Hence it can be summarised that many metal complexes, show superb activity against fungus*Candidaalbicans* and adequate activity againstvarious other species of fungus.

5. OTHER BIOLOGICAL ACTIVITIES OF METAL COMPLEXES:

Medication of infectious diseases emerged as challenging problem due to combination of factors such as coming up of new infectious diseases and the increasing number of microbial pathogens becoming multi-drug resistant. Resistance of drugs was first of all noticed in antimalarial drugs, first to chloroquine and afterward to others, in 1950s[58]. Incorporation of metal ions in drugs play a decisive role in numerous widely differing biological activities and on the basis of their concentration, they can contribute to the health of the organism or cause toxicity.[61-64]Along with the antifungal potential, some flouroquinolones-metal complexes exhibited anticancer, antibacterial, antiviral and anti- inflammatory activities[58]. Various research papers published the other biological effects of these complexes, such as antifungal, *antiparasitic, anticancer, antiinflammatory, antioxidant, and even insulin-mimetic effect*.[65-68]A low molecular weight copper complexes of quinolones have been found to show positive effects against several diseases such as*rheumatoid, gastric ulcers, tuberculosis, , and cancers*.[69-72]The anticancer activity of fluoroquinolones metal complexes has beenstudied and examined extensively in the past few years, depending on their capability to block topoisomerase II, thus supressing its activity to repair DNA[57-60]. The cytotoxic activity of the fluoroquinolones and their gold(III) complexes was tested against various cancer and tumour cells and the complexes were found more active than their corresponding free ligands[73]. Metal complexes have also been used as *antidote* since 1945, for intoxicationoccuring from therapy or household contamination or to increase the excretion of radioactive element. These antidotes donot cause much depletion of the body's essential metals and thus act as effective antidotes[74].Flouroquinolone-metal complexes can also be used for detection method. Their complexes with Tb^{3+} and Eu^{3+} exhibit strong luminescence and chemiluminescent properties, which are highly helpful for *analytical applications*.[75,76] The detection method based on the interactions of the parent drug and metal ion, have been tested for presence of Enrofloxacin[77,78], trovafloxacin[79], Ciprofloxacin[80], Ofloxacin[81], Levofloxacin[82] or Gatifloxacin[83]in the biological system.

6. CONCLUSION:

Infectious diseases have become global health threat, due to spread of microorganisms resistant to majority of treatments currently in use. Appearanceand spread of bacterial resistance, fungi resistant, viruses, and protozoan parasites to currently acessible antimicrobial drugs, threaten to send humankind back to pre-antimicrobial era. Hence, there is a critical need to create novel antimicrobials as well as to introduce into practice new innovative treatment options to fight against both drug-sensitive and drug-resistant microbes. Flouroquinolone-metal complexes are step ahead in this path. Flouroquinolones can bind to several divalent

and trivalent metal ions, which result in alteration of their biologicalactivity.Antifungal activities of Flouroquinolone- metal complexes are studied in this review paper and are compared with the flouroquinolones. It is found thatNorfloxacin and Levofloxacin along with its metal complexes donot show any antifungal behaviour whereas metal complexes of few drugs such asLomefloxacin, Sparfloxacin,Gatifloxacin, GemifloxacinandOfloxacin,showsignificant behaviour against various fungi when compared with the respective drug. These metal complexes not only come up as efficient bacteriocidal and antifungal agent, but also found to have anti-inflammatory, antivirus and anticancer activities.

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FIGURES

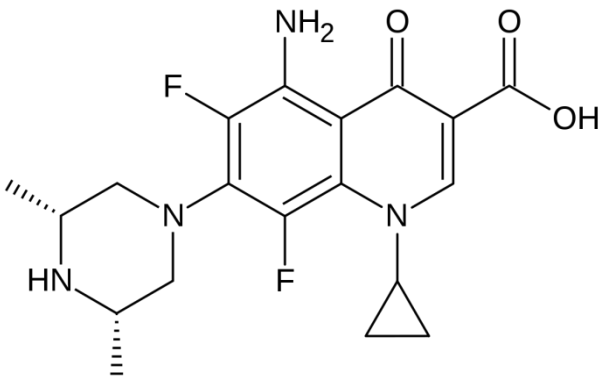

Fig. 1: A Flouroquinolone

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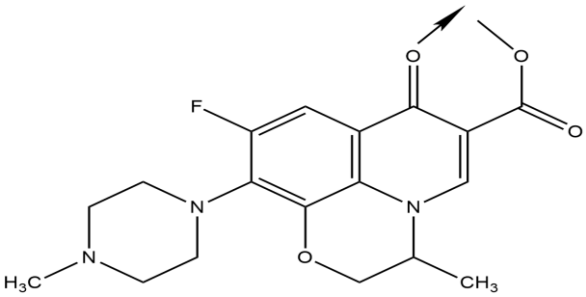

Fig. 2: Ligand coordinated through carbonyl oxygen and carboxylate oxygen.

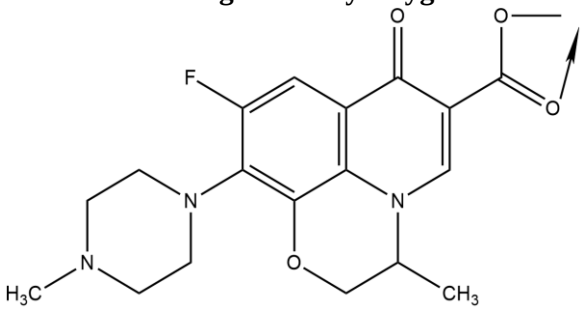

Fig 3 : Ligand coordinated through both the carboxylic group oxygen

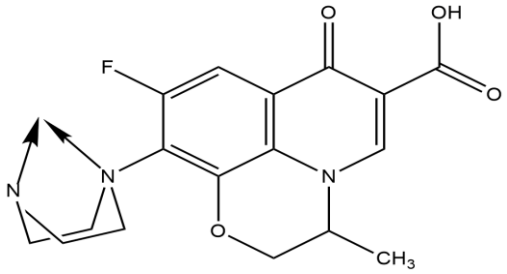

Fig 4: Ligand coordinated through through both piperazinic nitrogen atom

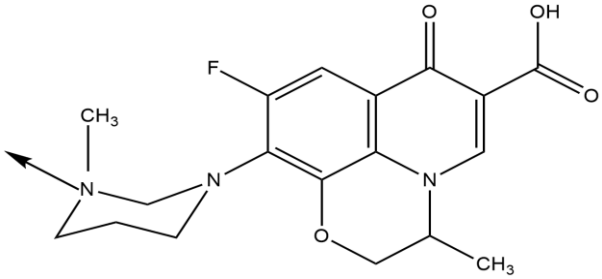

Fig 5 : Ligand coordinated through terminal piperazinyl nitrogen

TABLES

Table 1: Zone of inhition of GATIFLOXACIN and its metal complexes against few Fungi.

Zone of inhibition, +++++ represent excellent activity (150–200% inhibition); ++++ represent good activity (90–100% inhibition); +++ represent moderate activity (75–85% inhibition); ++ represent significant activity (50–60% inhibition); +, negligible activity (20–30% inhibition); n.a., no activity. size of disc: 6 mm (diameter)					
	T. rubrum	C. albicans	F. Solani	S. Cerevisia	REFERENCE
Gati	++++	++++	++++	ND*	[31]
Mg-gati	N.D.	N.D.	++++	ND	
Ca-gati	N.D.	+++++	++++	ND	
Cr-gati	+++++	+++++	+++	ND	
Mn-gati	+++++	N.D.	++++	ND	
Fe-gati	+++++	+++++	+++++	ND	
Co-gati	+++++	+++++	++++	ND	
Ni-gati	++++	+++++	++++	ND	

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Cu-gati	+++++	+++++	++++	ND
Zn-gati	+++++	+++++	++++	ND
Cd-gati	+++++	+++++	+++++	ND

* NOT DETECTED

Table 2: Zone of inhibition of GEMIFLOXACIN and its metal complexes against few Fungi.

Inhibition diameter zone values (mm) for GMFX, Phen and its metal complexes.				REFERENCE
	C. Albicans	A. awamori	Alternariasps	[32]
GEMI	21	ND	ND	
Zn(phe)gemi	22	ND	ND	
Zr(phe)gemi	17	ND	ND	
La(phe)gemi	25	ND	ND	
Ce(phe)gemi	19	ND	ND	
Th(phe)gemi	23	ND	ND	
U(phe)gemi	20	ND	ND	
Inhibition diameter zone values (mm) for GMFX, Bipy and its metal complexes.				REFERENCE
	C. Albicans	*A. awamori*	*Alternariasps*	[33]
GEMI	21	ND	ND	
Zn(bipy)gemi	20	ND	ND	
Zr(bipy)gemi	22	ND	ND	
La(bipy)gemi	19	ND	ND	
Ce(bipy)gemi	24	ND	ND	
Th(bipy)gemi	23	ND	ND	
U(phe)gemi	25	ND	ND	

Table 3: Zone of inhibition of OFLOXACIN and its metal complexes against few Fungi.

Diameter of zone of inhibition in mm,		REFERENCE	Diameter of zone of inhibition in mm,		REFERENCE	Diameter of zone of inhibition in mm,		REFERENCE
	T. Rubrum	34		*C. Albicans*	35		*C. Albicans*	36
OFLX	0		OFLX	15		OFLX	16	
Metronidazole	24		Zn(bipy)oflx	23		Zn(phe)oflx	20	
Ni(Met)oflx	40		Zr(bipy)oflx	18		Zr(phe)oflx	21	
Co(Met)oflx	34		Ce(bipy)oflx	20		UO(phe)oflx	17	
Mn(Met)oflx	20		Th(bipy)oflx	22				
Zn(Met)oflx	40		U(bipy)oflx	17				
Cu(Met)oflx	38							

Table 4: Antifungal activities of LEVOFLOXACIN, NORFLOXACIN and OFLOXACIN and their metal complexes.

	A. Flavus	A. Fumigatus	C. albicans	A awamori	Alternarias ps	REERENCE
LEVO	ND	ND	--	--	--	37
(Ti,V,Zr,Y,Ce,U)levo	ND	ND	--	--	--	

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NFLX	--	--	ND	--	--	38
(Mn,Co,Ni,Cu,Zn) nflx	--	--	ND	--	--	
OFLX	--	--	--	--	ND	39
(Zn,Zr,U,Ce,Th,U) oflx	--	--	--	--	ND	

Table 5: Zone of inhibition of LOMEFLOXACIN and its metal complexes against few Fungi

Inhibition zone diameter in mm/mg by disk diffusion method and Amphotericin-B is taken as standard					
	C.Albicans	A. Niger	A. Flavus	S. Cerevisiae	REFERENCE
LOME	11	--	ND	--	84
Amphotericin B	19		16		
Cr(lome)	12	--	ND	--	
Mn(lome)	11	--	ND	--	
Fe(lome)	13	--	ND	--	
Co(lome)	20	--	ND	--	
Ni(lome)	21	--	ND	--	
Cu(lome)	12	--	ND	--	
Zn(lome)	12	--	ND	--	
Th(lome)	12				
UO_2(lome)	12				

Table 6: Zone of inhibition of SPARFLOXACIN and its metal complexes against few Fungi

Inhibition zone diameter in mm/mg by disk diffusion method and Amphotericin-B is taken as standard			
	A.flavus	C. albicans	REFERENCE
SPAR	0	0	85
Amphotericin-B	16	19	
Cu(spar)	15	18	
Co(spar)	13	12	
Ni(spar)	14	12	
Mn(spar)	0	0	
Cr(spar)	0	0	
La(spar)	0	0	
Fe(spar)	0	0	
UO^2(spar)	0	0	
Cu(spar)alanine	0	0	
Co(spar) alanine	14	17	
Ni(spar) alanine	13	12	
Mn(spar) alanine	0	0	
Cr(spar) alanine	0	0	
La(spar) alanine	0	0	
Fe(spar) alanine	0	0	
UO^2(spar) alanine	0	0	