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Abstract

According to World Health Organization (WHO) infectious diseases are spreading faster and emerging more quickly than ever before. Due to the increasing incidents related with new and reemerging infectious diseases, discovery and development of new antimicrobial compounds with diverse structures and action mechanism is urgently needed. The antibacterial effects of lanthanides (Ln) have been studied since the 19th century and have been employed since then with more or less success in treatment of various diseases. This review gathers together all the studies dealing with the antimicrobial activity of Ln(III) complexes published until now. Overall, it was discovered that the antimicrobial activity of the Ln complexes is greater than the activity of the free ligand (L), indicating that the complexation with the Ln enhances the activity of the L. In some cases Ln complexes exhibit antimicrobial activity similar or even better than the activity of standard antimicrobial agents. These results are encouraging, Ln complexes representing a possible alternative to antimicrobial agents used currently.

Keywords: Ln(III) complexes, antibacterial activity, Schiff base, antifungal activity, complexation theory

Abbreviations: WHO, World Health Organization; Ln, lanthanide; K, ligand; G (+), Gram positive; G (-), negative; La, Lanthanum; Ce, Cerium; Pr, Praseodymium; Nd, Neodymium; Pr, Promethium; Sm, Samarium; Eu, Europium; Gd, Gadolinium; Tb, Terbium; Dy, Dysprosium; Ho, Holmium; Er, Erbium; Tm, Thulium; Yb, Ytterbium; Lu, Lutetium; Y, Yttrium; MIC, Minimal Inhibitory Concentration; *BS, Bacillus subtilis: SL, Sarcina lutea; SA, Staphylococcus aureus; PD, Pneumoniae diplococcus; EC, Escherichia coli; EH, Enterococcus hirae; PA, Pseudomonas aeruginosa; KP, Klebsiella pneumonia; AN, Aspergillus niger; ST, Salmonella typhi; CA, Candida albicans; SC, Staphylococcus cure; VC, Vibrio cholera; AF, Aspergillus fumigatus; BC, Bacillus cirroflagellosus; PN, Penicillium notatum; SC, Saccharomyces cerevisiae; BM, Bacillus megaterium; AF, Aspergillus flavus; KO, Klebsiella oxytoca; BO, Brevibacterium otitidis; TM, Trichophyton mentagrophytes; ML, Micrococcus luteus; ENT, Enterococcus; BAC, Bacillus; BAC C, Bacillus cereus; AB, Acinetobacter baumannii; SP, Salmonella paratyphi; FO, Fusarium oxysporu; PC, Pencillium chrysogenum; PP, Proteus penneri; EF, Enterococcus faecalis; SM, Serratia Marcescens; PV, Proteus vulgaris; PM, Penicillium Marneffei; PI, Penicillium italicum; SR, Syncephlastrum racemosum; AA, Alternaria alternate; SD, Shigella dysenteriae; PrM, Proteus mirabilis; SE, Salmonella enteritidis; Spy, Streptococcus pyogenes; CP, Curvularia pallescens; CC, Colletotrichum capsici; CT, Candida tropicalis.*

Introduction

Infectious diseases cause widespread morbidity and mortality worldwide regardless of all the improvements achieved in sanitation, vaccine development and other public health measures [1]. Despite all the efforts done, infectious diseases appear far from being eradicated. In the last decade, as a consequence of the environmental changes and influence of global warming, increased movement of goods and persons and other phenomena concerning vectors and hosts, re-emerging of old infectious diseases and the development of new ones have been promoted [2]. Many infectious agents are particularly sensitive to climatic conditions in terms of faster proliferation and reproduction as a consequence of increased temperature, prolonged season in which the infection agents are spread between the hosts and also higher migration rate of human populations which are used as hosts by these infectious agents [3].

According to WHO, infectious diseases are spreading faster and emerging more quickly than ever before. Between 1940 and 2004 emergence of 335 infectious diseases has been reported, the majority being of bacterial or rickettsial (54.3 %) nature [2].

In the past decades there has been registered an increase in the antimicrobial drug resistance among bacteria and other pathogens, representing a real threat to the successful treatment of hospital- and community- acquired infections caused by Gram positive (G (+)) and Gram negative (G (-)) bacteria being recognized as a global public health emergency [4]. In this context, a global effort to develop novel antibiotics or alternative approaches to prevention and treatment is necessary.

This review is an extensive compilation of all the studies dealing with the antimicrobial (antibacterial and antifungal) activity of Ln(III) complexes published since 1995 until beginning of 2019.

Antimicrobial activity mechanism

After crossing the epithelial barrier, the infectious microorganisms spread throughout the body using the circulatory blood system from which they are removed by macrophages and trapped in phagosomes. The enzymes present in the phagosomes digest the trapped microorganisms via oxygen- dependent or oxygen-independent bacterial killing mechanisms [5]. Nevertheless, many microorganisms escape from the macrophage digestion or resist the killing mechanism thus complicating the eradication of intracellular infections.

An antimicrobial agent is a substance that is capable of killing the bacteria by binding to its vital metabolism compounds and thus obstruct the normal cellular activities by inhibiting the synthesis of functional biomolecules [5]. Some antimicrobials act only against a narrow range of bacteria while others kill a broad spectrum of G (+) and G (-) bacteria. Although great progresses have been made in the antimicrobial development, intracellular infectious diseases remain difficult to treat due to difficult transportation of the antimicrobials through cell membranes and their low activity inside the cells. Moreover, due to their toxicity toward healthy tissues, the antimicrobials use is significantly limited [5]. Another major issue is the acquired resistance of infectious microbes to antimicrobials consequently requiring the development of new alternative antimicrobial drug delivery strategies.

To function properly some types of antibiotics require the presence of metal ions which can be: (i) integral parts of the antibiotics structure and thus their removal results in deactivation of the antibiotics structure, or (ii) the binding of metal ions to the antibiotic molecules may provoke fundamental chemical and biochemical consequence, without affecting the antibiotics structure [6].

The antimicrobial properties of metals have been known for centuries and represented major breakthrough in medicinal field. In this context, the design and synthesis of organic–inorganic hybrid complexes based on coordinate bonds have attracted the interest of the research community working in the coordination chemistry field [7].

The antibacterial effects of Ln were first discovered in the 19th century when several Ce(III) salts (acetate, stearate, chloride, and nitrate) were reported to have antibacterial activity and the oxidizing properties of Ce(IV) led to the use of Ce(IV) sulfate as an antiseptic powder [8]. Since then Ln have been employed with more or less success for tuberculosis treatment, anticoagulants and anti-atherosclerotic compounds [8].

The Ln are the group of elements which include the elements from lanthanum (Z = 57) to lutetium (Z = 71) with an electronic configuration of [Xe]4f^{0} to [Xe]4f^{14}. Except Ce and Eu which can exist as Ce^{4+} and Eu^{2+}, most of the Ln are only stable in the trivalent form Ln^{3+}. These elements possess a particular property known as “Ln contraction” which consists in a decrease of the atomic size and radius with the increase of the atomic number [8].

Ln have similar ionic radii to calcium but due to their higher charge (Ln^{3+}) Ln ions have a high affinity for Ca^{2+} sites on biological molecules and therefore Ln^{3+} are able to block calcium channels. Thus, even though the Ln^{3+} ions themselves cannot cross cell membranes, they can act by blocking the exterior face of the calcium channel.

Since the Ln can substitute calcium in proteins [9], calcium dependent enzymes functioning can be affected by Ln either be inhibition, or by a superior activation [8].

Chelation theory

Most of the studies reported that the antibacterial activity of the metal complexes was superior to the activity of the free parental L. This type of behavior was explained considering Overtone's concept [10] and Tweedy's chelation theory [11].

The Overtone's theory regarding the cell permeability, the lipid membrane that surrounds the cell allows only the passage of lipidsoluble materials; therefore liposolubility is a key factor which controls antimicrobial activity. Upon chelation, the polarity of the metal ion will be reduced due to the overlap of the L orbital and partial sharing of the positive charge of the metal ion with donor groups. Furthermore, it increases the delocalization of π-electrons over the whole chelate ring and improves the lipophilicity of the metal complexes [12]. This increased lipophilicity favors the penetration of the metal complexes through the lipid membranes and blocks the metal binding sites in bacterial enzymes, thus disturbing the normal functioning of the cell. Moreover, these metal complexes disturb the respiratory processes of the cell by inhibition of energy production or ATP production or also by uncoupling of oxidative phosphorylation [13] and thus block the synthesis of proteins which restricts further growth of the organism and will finally lead to cell death.

It is difficult to stipulate the exact mechanism of the antimicrobial activity of metal complexes due to the complexity of biological systems; however the increased activity of the parental L after complexation with a metal ion is usually explained by the chelation theory.

Examples of Ln(III) complexes with antimicrobial activity

The examples gathered in this section are summarized in Table 1.

Table 1. Examples of Ln(III)-L complexes and their antimicrobial activity.

Ln(III)-Complex		**Antimicrobial activity tested**			
Ln(III)	**L**	**G (+)**	**G (-)**	**Fungi**	**Ref.**
La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III), Ho(III), Er(III), Yb(III), Y(III)	N-isonicotinamido-4-N-[(N-carboxy-methyl-N-phenyl)amino-acetyl]aminoacetophenonaldimin	*BS, SL, SA, PD,*	*EC, PA*	-	[14]
La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III), Y(III)	tetracycline	*SA*	*EC*	-	[16]

La(III), Gd(III), Lu(III)	morin	*SA*	*EC, KP*	-	[17]
Tm(III), Yb(III), Lu(III)	morin	*EH*	*EC*		
La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III), Y(III)	sulfamethoxazole	*SA*	*EC*	-	[21]
La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Dy(III), Tm(III), Yb(III), Lu(III)	2-(N-salicylideneamino)-3-carboxyethyl-4,5,6,7 tetrahydrobenzo[b]thiophene	*SA, SC*	*EC*	*CA, AN*	[22]
La(III), Ce(III), Pr(III), Nd(III), Sm(III), Dy(III)	2-pyrazinecarboxylic acid		*EC, ST, VC*	*AF, AN*	[23]
La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III), Y(III)	2-[2-hydroxy-3-methoxyphenyl]-3-[hydroxyl-3-methoxybenzylamino]-1,2-dihydroquinazoline- 4(3H)-one	*BC*	*PA*	*AN, PN*	[24]
La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III)	poly[(2-hydroxy-4-methoxy benzophenone) ethylene] resin	*BS, SA*	*EC*	*SC*	[25]
La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Dy(III), Yb(III), Lu(III)	2-(N-indole-2-onone)amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[b]thiophene	*BM*	*VC, ST*	-	[26]
La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III)	[(2-hydroxybenzaldehyde)-3-isatin]bishydrazone)	-	-	*CA, AN, SC, PN*	[27]
La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III)	polymer HEAP-ED (2-Hydroxy-4-ethoxy acetophenone and ethane diol)	*BS, SA*	*EC*	*SC*	[28]
La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III)	polymeric resin (condensation of 2-hydroxy-4-ethoxybenzophenone with 1,2-propylene glycol)	*BS, SA*	*EC*	*SC*	[29]
La(III), Pr(III), Nd(III), Gd(III)	bis(benzimidazole-2`-yl-methyl)amine	*BC*	*PA*	*AN, PN*	[30]
Ce(III)	H_3L (condensation of thiocarbohydrazide with 2-hydroxy-1-naphthaldehyde)	*SA*	*EC*	*CA, AF*	[31]
La(III)	Sparfloxacin (5-amino-1-	*SA*	*EC*	*AF, CA*	[32]

	cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3 quinoline carboxylic acid), DL-alanine				
Ce(IV)	moxifloxacin	*BO, BS, SA*	*EC, PA, KO*	-	[34]
Pr(III), Nd(III), Sm(III), Eu(III), Er(III)	2,6-pyridine dicarboxylic acid and picolinic acid	*SA*	*EC*	-	[35]
La(III), Ce(III)	Norfloxacin	*SA, BS*	*EC, PA*	*AF, CA*	[6]
La(III), Sm(III), Eu(III), Tb(III), Dy(III)	2,4,6-tri(2-pyridyl)-s-triazine	-	*EC*	-	[37]
La(III)	4-(R)-cinnamate (4-Rcinn, R = H (1), MeO (2), Cl (3)) and 4-methoxyphenylacetate L (4)	-	-	*CA, AN, TM*	[40]
Dy(III)	1,10-phenanthroline	*ML, ENT, BAC, BAC C*	*SM, KP, EC, Shigella, AB, SP B, C*	-	[41]
Yb(III)	1,10-phenanthroline	*ML, BAC, BAC C, ENT*	*SM, KP, EC, Shigella, AB, SPB, C*	-	[42]
Y(III)	1,10-phenanthroline	*ML, BAC, BAC C*	*SM, KP, EC, Shigella, AB, ENT, SPB, C*	-	[43]
Er (III), Tb (III), Dy (III)	3-bromo-5-iodobenzoate, 1,10-phenanthroline	*SA*	*EC*	*CA*	[44]
Eu(III), Gd(III), Nd(III), Sm(III), Tb(III)	phenylthioacetic acid	*BS, SA*	*EC, PA*	*AN, AF, CA*	[45]
La(III), Pr(III), Nd(III), Sm(III), Ho(III)	phenylthiopropionic acid	*BS, SA*	*EC, PA*	*AN, AF, CA*	[46]
La(III), Pr(III), Nd(III), Gd(III)	[1,2-bis(benzimidazole-2-yl)ethane dihydrochloride], [1,4-bis(benzimidazole-2-onium)butane dihydrochloride]	*BC*	*PA*	*AN, PN*	[47]
Tb(III), Dy(III), Er(III), Yb(III)	3,5-dimethoxybenzoic acid, 1,10-phenanthroline	*SA*	*EC*	*CA*	[48]
La(III)	NC_5H_5 or $P(C_6H_5)_3$, $N_2C_{12}H_8$ or	*BAC C*	*KP*	*FO*	[49]

	$N_2C_{10}H_8$				
La(III), Ce(III), Pr(III), Nd(III), Sm(III)	4-butyl-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione	*SA* (MTCC-96), *BAC C* (MTCC-430), *PC*	*EC* (MTCC-433), *ST* (MTCC-733), *VC* (MTCC-3906)	*AF, AN CA* (MTCC-183)	[50]
Ce(III), Nd(III), Sm(III), Eu(III)	3,5,13,15,21,22-hexaaza-2,6,12,16-tetramethyl-4,14-dithiatricyclo[15.3.1.1(7-11)]docosane-1(21),2,5,-7,9,11(22),12,15,17,19-decaene	-	-	*AN, FO*	[51]
Sm(III), Tb(III)	2-aminobenzoic acid, 2-amino-5-chlorobenzoic acid	*SA*	*EC*	*AF, AN*	[52]
La(III), Ce(III), Sm(III), Y(III)	pyridoxine mono hydrochloride	*SA, BS*	*EC, PA*	*AF, CA*	[53]
La(III), Ce(III), Sm(III), Y(III)	Enalapril maleate	*SA, BS*	*EC, PA*	*AF, CA*	[54]
Eu(III), Yb(III)	4,4,4-trifluoro-1(2-napthyl)-1,3-butanedione, 4,4,5,5,6,6,6-heptafluoro-1-(2-thienyl)-1,3-hexanedione, hexafluoroacetylacetonate, Phendione	*SA*	*EC, PP*	-	[55]
Ce(III), Sm(III), Y (III)	*Metformin* hydrochloride	*SA, BS*	*EC,PA*	*AF, CA*	[56]
Ho(III), Nd(III), Sm(III), Dy(III), Eu(III), Tb(III), Yb(III), Er(III)	3,4-dichlorobenzoate, 1,10-phenanthroline	*SA*	*EC*	*CA*	[57]
Tb(III)	2-hydroxy-4,6-dimethoxyace tophenone, 2,2-biquinoline or 5,6-dimethyl-1,10-phenanthroline or bathophenanthroline	*SA* (MTCC 3160), *BS* (MTCC 441)	*EC* (MTCC 443)	*CA, AN*	[58]
Eu(III)	1,10-phenanthroline	*SA* (ATCC 25923), *EF* (ATCC 11700)	*EC* (ATCC 25922),*PA* (ATCC 27853)	-	[59]
La(III)	1,10-phenanthroline	*ML, BAC C, BAC*	*SM, Shigella, AB, KP, SPC, SPB, EC,*	-	[60]

			ENT		
Ce(III)	1-ethyl-4-hydroxy-3-(nitroacetyl)quinolin-2(1H)-one	*SA*	*KP, EC, PV*	*CA*	[61]
La(III), Pr(III), Nd(III), Gd(III)	2,2'-iminobis [N-(3-hydroxypropyl)acetamide]	*SA, BS*	-	*CA, PM*	[62]
Sm (III), Eu (III), Gd (III)	N-phenylanthranilic acid, 1,10-phenanthroline	*SA* (ATTCC 6538)	*EC* (ATCC 10538), *PA* (ATCC 15442)	-	[63]

In 1995, Shen et al. synthesized thirteen Ln(III) complexes $LnL_3 \cdot 6H_2O$ (where Ln = La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III), Ho(III), Er(III), Yb(III), Y(III); HL = N-isonicotinamido-4-N-[(N-carboxy-methyl-N-phenyl)amino-acetyl]aminoacetophenonaldimin (Figure 1) and tested their antibacterial activity against the standard strains of G (+) bacteria *(BS, SL, SA, PD)* and G (-) bacteria *(EC*, *PA)* was determined using the plate method [14].

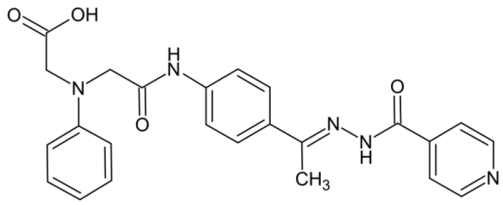


Figure 1. N-isonicotinamido-4-N-[(N-carboxy-methyl-N-phenyl)amino-acetyl]aminoacetophenonaldimin [14].

The results showed that the L was inactive against the tested bacteria (except against *EC*), while the La(III), Pr(III), Sm(III), Tb(III) and Yb(III) complexes showed some inhibiting activity against them. The authors concluded that the enhanced activity of the complexes compared to the free L may be due to the effect of metal ions on the cell, as indicated by a previous study in which complexes of Cu(II), Ni(II) and Co(II) with 3-benzoyl-1-[2-N-(substituted-2'-thienyl methylmethylene/methylene)] prop-2-ene-1-oic acid hydrazides showed antibacterial activity as a result of coordination of the L with the metal ions [15].

Karthikeyan et al. prepared a series of Ln(III) tetracycline complexes of the type $[Ln(TC)Cl_3] \cdot 2H_2O$ [Ln = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III) and Y(III); TC = tetracycline] (Figure 2) which were evaluated against the G (+) *(SA)* and G (-) (*EC*) bacteria using the serial dilution technique [16].

The results obtained in this study indicated that Ln tetracycline complexes are more toxic against G (+) organisms (*SA*), than the G (-) organism (*EC*). Against the G (+) organism, the L showed an activity of 88.4 % of bacterial growth inhibition, compared to 90–100 % of the Ln

complexes, while against G (-) organism the L exhibited activity of 67.5 % compared to 23–40 % of its Ln complexes [16].

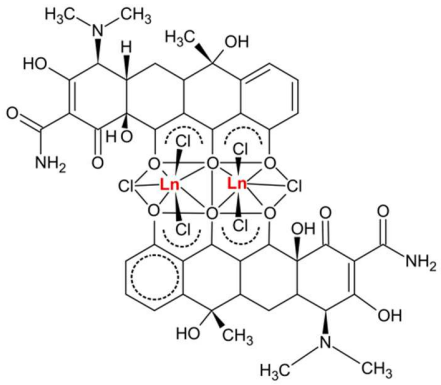


Figure 2. The most probable molecular shape of the Ln–tetracycline complex [16].

In a study of Kopacz and collaborators, the antibacterial activity of morin (Figure 3), morin-5'-sulfonic acid sodium salt (NaMSA) and the complexes of La(III), Gd(III) and Lu(III) with morin were tested against G (-) (*EC*, *KP)* and G (+) (*SA*) and compared with the activity of the standard antibacterial agent Penicillin [17].

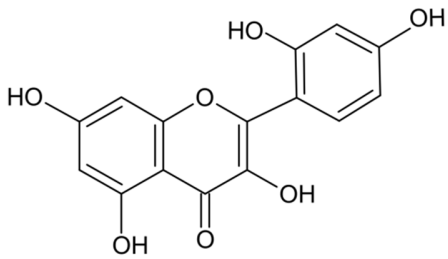


Figure 3. Morin structure [18]**.**

In order to determine the antibacterial activities, two methods were employed: (i) dilution method which determined the Minimal Inhibitory Concentration (MIC) and (ii) cylinder-plate diffusion method which measured the bacteriostatic diameter and compared [18]. The obtained activities were compared with the antibacterial activity of *Penicilin*. The results showed that morin completely inhibited the bacterial growth *EC* and *SA*. La(III) complex exhibited the same activity as morin against *EC*, while against *SA,* both La(III) and Gd(III) complexes showed a similar activity. Gd(III) complex was the only one showing inhibitory effect on *KP* when concentrations higher than 0.3 µg/mL were used. When the inhibition diameter was measured, the results showed that at a concentration of 10 µg/cylinder the Ln complexes showed higher activity than morin alone, while at concentration of 100 µg/cylinder morin was the most effective inhibitor [18].

Later in 2017, Woźnicka and collaborators published an article dealing with antibacterial activity of Tm(III), Yb(III) and Lu(III) complexes with morin (Figure 4). The antibacterial activity of morin and its complexes was determined by cylinder-plate diffusion and the dilution methods against G (-) (*EC)* and G (+) (*EH)* and compared with the standard antibacterial agent *Ampicilin*.

Both morin and its complexes were less active than *Ampicilin* against *EC*, while against *EH* none of them were active. The lowest MIC value (250 µg/ml) against *EC* was obtained for morin, while the Yb(III) and Tm(III) complexes exhibited the same activity (MIC = 500 µg/ml). Lu(III) complex presented the highest MIC value (1000 µg/ml) and also the highest inhibition zone (16 mm) for this concentration. Although Lu(III) gave the highest inhibition zone, it is not a clear indication of a higher antibacterial activity of this complex. This result may be attributed to other factors such as the rate of diffusion of the antibacterial agents and the amount of bacterial isolates present in a certain amount of agar solution [19].

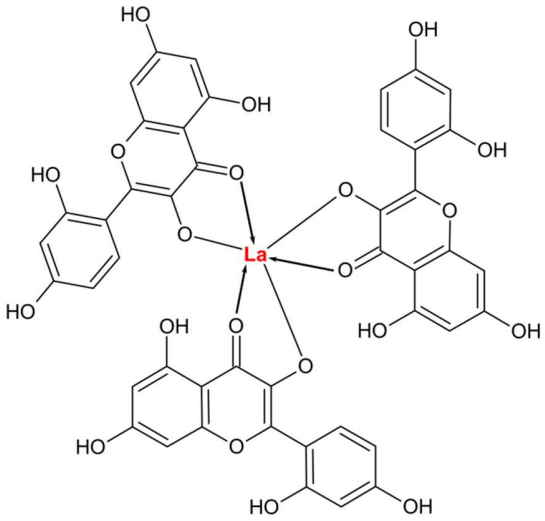


Figure 4. Proposed structure of complexes of lanthanide ions with morin in solid state (Ln = Tm, Yb and Lu) [20].

In 2006 Karthikeyan and collaborators published an article dealing with synthesis of nonelectrolytic Ln(III) complexes $[LnL_2Cl_3]\cdot 2H_2O$ (Ln = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III), and Y(III)) containing sulfamethoxazole L (Figure 5) [21].

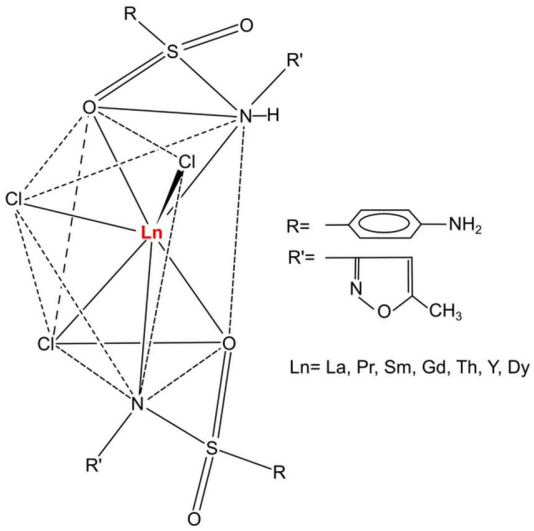


Figure 5. Proposed structure for Ln(III) complexes of sulfamethoxazole [21].

The antibacterial activity of the sulfamethoxazole L and its Ln(III) complexes were determined against the bacteria G (-) (*EC)* and G (+) (*SA*) employing the serial dilution technique. Both the L and Ln–sulfamethoxazole complexes were more toxic against G (+) organism than the G (-). Against the G (+) organism the L showed an activity of 44.17 % of bacterial growth inhibition whereas the Ln complexes produced 54.3–90.2 % inhibition, while for G (-) organism the L exhibited higher activity (89.2%) compared to its Ln complexes (42.2–59.1 %) [21].

In another study, Mohanan et al. prepared Ln(III) complexes of the type $[Ln(HSAT)_2(H_2O)_3Cl_3]$ and $[Ln(HSAT)_2(NO_3)_3]$ where Ln = La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Dy(III), Tm(III), Yb(III), or Lu(III), and HSAT = 2-(N-salicylideneamino)-3-carboxyethyl-4,5,6,7 tetrahydrobenzo[b]thiophene (Figure 6) [22].

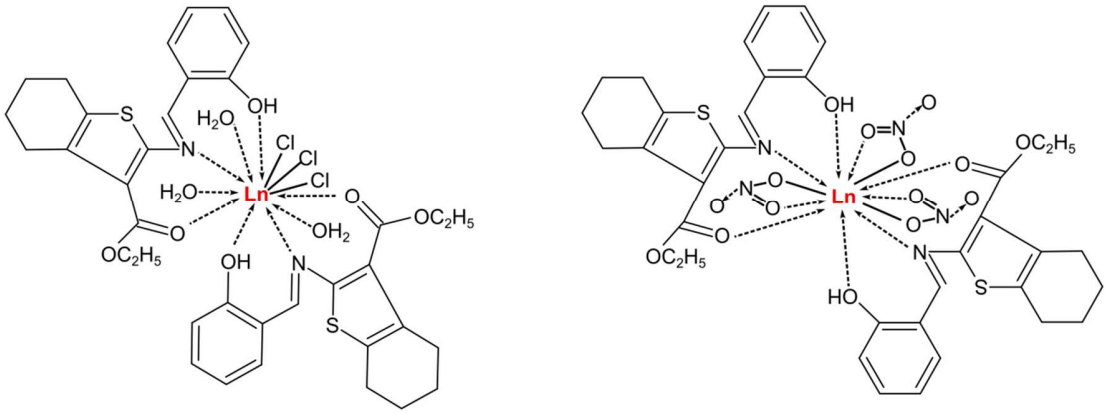


Figure 6. Structure of the aquachloro complex $[Ln(HSAT)_2(H_2O)_3Cl_3]$ (left) nitrato complex $[Ln(HSAT)_2(NO_3)_3]$ (right) [22].

Their antibacterial against G (-) (*EC), G (+) (SA, SC*) and antifungal activities (against *CA* and *AN*) were determined and it was concluded that L is physiologically active and chelation with Ln enhances its activity. The authors explained the enhanced activity the complexes using the chelation theory which states that the chelation reduces the polarity of the metal ion thus considerably increasing the lipophilic character of the chelate. As a result, the interaction between the metal ion and lipid from the cell wall is favored leading to the breakdown of the permeability barrier of the cell and thus resulting in interference with the normal cell processes [22].

The higher toxicity of the metal complexes compared to the L was also attributed to the interaction of metal ions with cellular components since all the complexes contain a variety of functional groups that can act as metal-binding L [22]. The nitrate complexes exhibited less inhibition as compared to the aquachloro complexes due to the binding capacity of the nitrate ion toward the central metal ion which is greater than that of the chloro complex. As a consequence less metal ion is available to act as antibacterial agent. Moreover, the complexes can also form hydrogen- bonded interaction through the coordinated anions with the active centers of the cell constituents resulting in interference with the normal cell processes.

The authors conclude that the antimicrobial properties possessed by these Ln compounds is a complex combination of several factors like: chelation, the metal ion L nature, coordinating sites, geometry of the complex, concentration, hydrophilicity, lipophilicity, steric and pharmacokinetic factors and other environmental factors [12].

In their study, Premkumar and Govindarajan synthesized hydrazinium Ln metal complexes of 2-pyrazinecarboxylic acid (HpyzCOO) with formulas $(N_2H_5)_2[Ln(pyzCOO)_5]\cdot 2H_2O$, (Ln = La(III) or Ce(III)) and $(N_2H_5)_3[Ln(pyzCOO)_4(H_2O)]\cdot 2NO_3$ (Ln = Pr(III), Nd(III), Sm(III) or Dy(III)) [23]. The antibacterial activity of the free acid and its Ln complexes was carried out against G (-) bacteria (*EC, ST, VC)* and their antifungal activities were determined against *AF* and *AN* using the disc diffusion method. Ln complexes showed enhanced activity compared to the free L and its hydrazinium salts, behavior explained using the chelation theory described previously.

All the Ln complexes exhibited better activities compared to the activity of standard antibiotics (*Co-trimoxazole* and *Carbendazim*) with greater inhibition zone at all concentrations (1 %, 2 %, 4 %) tested except Ce(III), Sm(III), Nd(III) and Dy(III) complexes, which showed almost equal or no activity against *EC* at 1 % concentration. In the case of antifungal activity, the complexes showed lower activity at 1 % concentration similar activity with the standard at 2 and 4 % concentrations [23]. The results of this study indicate that that all the complexes were more efficient against bacteria rather than fungi.

Antimicrobial activity of Ln(III) complexes with 2-[2-hydroxy-3-methoxyphenyl]-3-[hydroxyl-3-methoxybenzylamino]-1,2-dihydroquinazoline- 4(3H)-one (Hmpbaq) was studied by Gudasi et al. [24]. The interest for the Hmpbaq L (Figure 7) arises from the fact that it possesses multiple coordinating sites and therefore it may act as a monodentate, bidentate or tridentate specie.

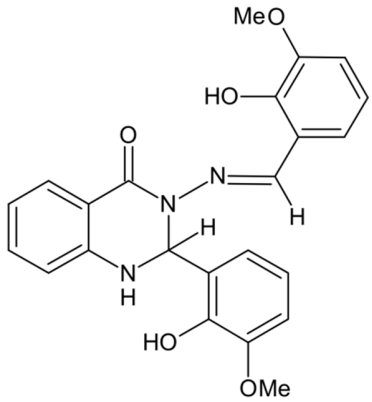


Figure 7. Structure of the Hmpbaq L [24].

The L, metal salts, and the corresponding complexes were tested for their antibacterial activity against G (-) (*PA)*, G (+) (*BC)* bacteria and antifungal activity against the pathogenic fungi *AN* and *PN* employing the cup-plate method. The results showed that the L Hmpbaq had low activity against *PN, PA*, and *BC* except against *AN* where it has shown moderate activity. On the contrary all the complexes La(III), Pr(III), and Nd(III) ones were moderately efficient against *PA* and showed moderate activity against *BC* [24].

The proposed structure for the Ln(III) complexes (Figure 8) having the general formula $[Ln(mpbaq)_2(H_2O)_2]\cdot NO_3$ (Ln = La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III), and Y(III)) described in this study showed enhanced antibacterial activity compared to the L whereas no variation was observed in case of antifungal activity [24].

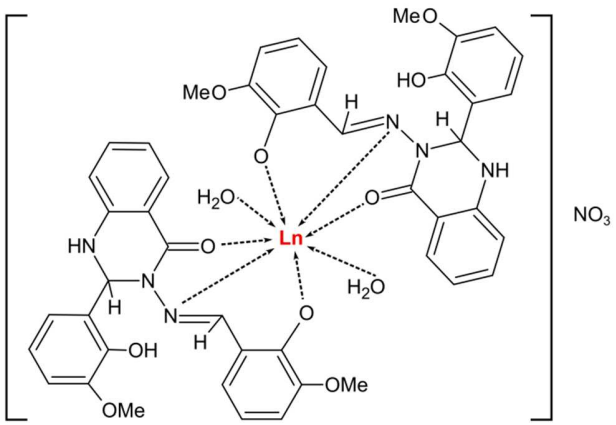


Figure 8. Proposed structure of Ln(III) complex [24].

In another study poly[(2-hydroxy-4-methoxy benzophenone) ethylene] resin and its polychelates with Ln (Ln(III) = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III)) (Figure 9) were synthesized and their antimicrobial activity against bacterial strains of G (-) (*EC)*, G(+) (*BS*, *SA)* and yeast strains *SC* were tested employing the agar diffusion method [25].

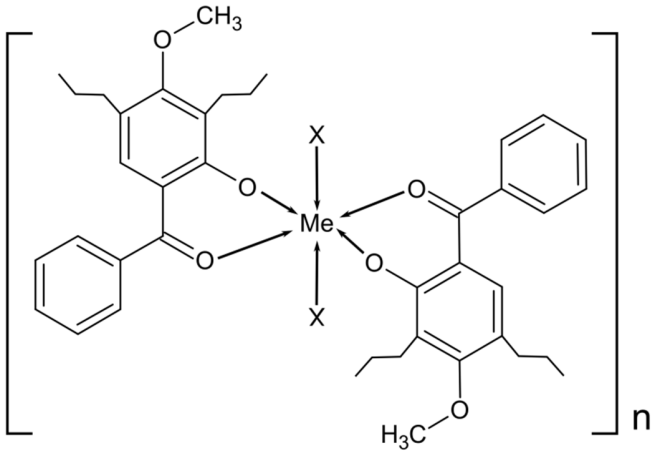


Figure 9. Proposed structure of the polymeric chelate, where Me = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III), X = H_2O [25].

Several concentrations between 50 and l000 ppm were tested and it was found that 500 ppm was the minimum concentration of the L and the polychelates necessary to inhibit the microbial growth. In comparison to the free polymeric L, polychelates showed significantly improved antibacterial activity against some bacterial species [25].

In the same year Thankamony and Mohanan published an article dealing with the synthesis and the antibacterial activity of Ln (La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Dy(III), Yb(III), Lu(III)) nitrate complexes of 2-(N-indole-2-onone)amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[b]thiophene [26].

The synthesis of complexes (Figure 10) prepared in this study were obtained by the general equation:

$$Ln(NO_3)_3 \quad + ISAT \rightarrow [Ln(ISAT)(NO_3)_3]$$

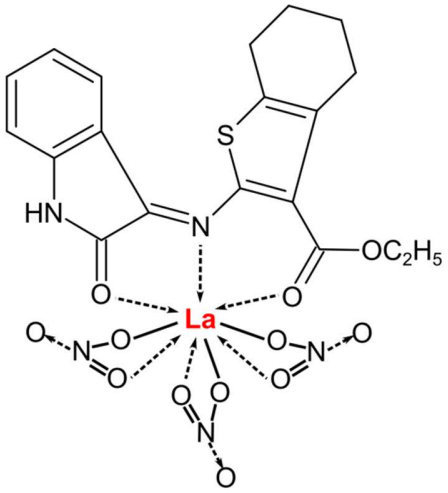


Figure 10. Proposed structure of the Ln(III) complexes with 2-(N-indole-2-onone)amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[b]thiophene [26].

The antibacterial activity of these Ln(III) complexes and the free L were screened against G (-) (*VC, ST)* and G (+) (*BM)* and the results showed that all the complexes were more active than the free L [26] due to chelation and other factors as explained before by Mohanan et al. [22].

In 2008 Mohanan et al. published another article regarding the complexes of the type $[Ln(HISA)_2Cl_3]$ (where Ln (III) = La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), or Gd(III) and HISA= [(2-hydroxybenzaldehyde)-3-isatin]bishydrazone) (Figure 11) and their antifungal activity against *CA*, *AN*, *SC* and *PN* [27].

Their results indicated that the antifungal activity of the L increased upon chelation with Ln metals. The most active complex was La(III) which showed 100 % inhibition of all the tested fungi, followed by Gd(III) which showed 100 % inhibition of *CA* and *PN* and 75 % inhibition for the other two fungi. Nd(III) complex also showed 100 % inhibition of *AN* and *SC* while for the *CA* the inhibitory activity was 75 % and 50 % for *PN* [27].

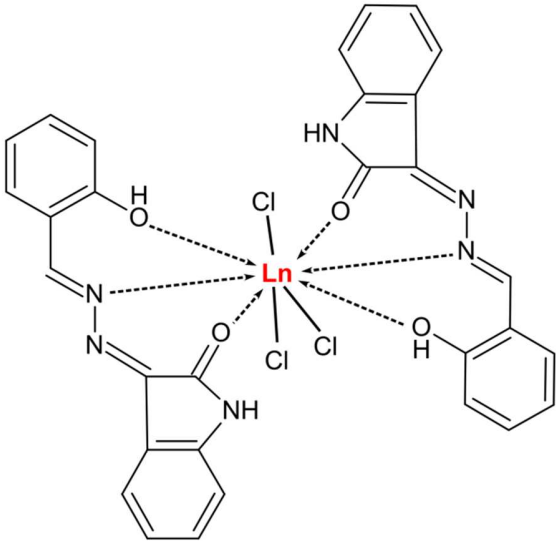


Figure 11. Structure of the Ln complexes [27].

Coordination polymers of HEAP-ED with La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III) metal ions (Figure 12) have been synthesized by Kapadia et al [28]. Their antimicrobial activity was determined against G (-) (*EC),* G (+) *(BS, SA*) bacterial strains and also one yeast strain (*SC)* using agar diffusion method.

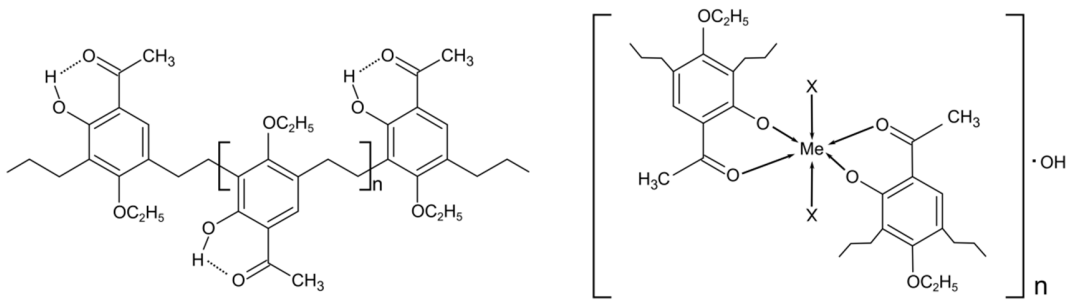


Figure 12. Proposed structure of the polymeric L (left) and polymeric chelate (right) (Me = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III); X = H_2O [28].

Concentrations between 50 and l000 ppm were tested and it was found that the minimum concentration of the L and coordination polymers which inhibits the microbial growth was 500 ppm. Though the polymeric L had moderate activity against *SC,* the coordination polymers obtained upon chelation with Ln metals showed significantly improved activity in comparison to the free polymeric L against all bacterial species, [28].

In another study the same authors prepared a different polymeric L (resin) (Figure 13) by condensation of 2-hydroxy-4-ethoxybenzophenone with 1,2-propylene glycol and its chelates with Ln(III) [29].

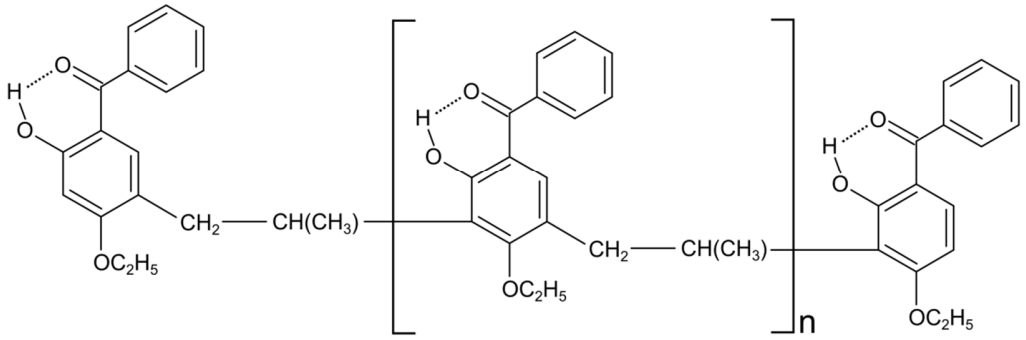


Figure 13. Proposed structure for the polymeric L [29].

The antimicrobial activity of the resin and its polychelates (Figure 14) was evaluated against the G (-) (*EC),* G (+) *(BS*, *SA)* bacterial strains and the *SC* yeast strain using agar diffusion method.

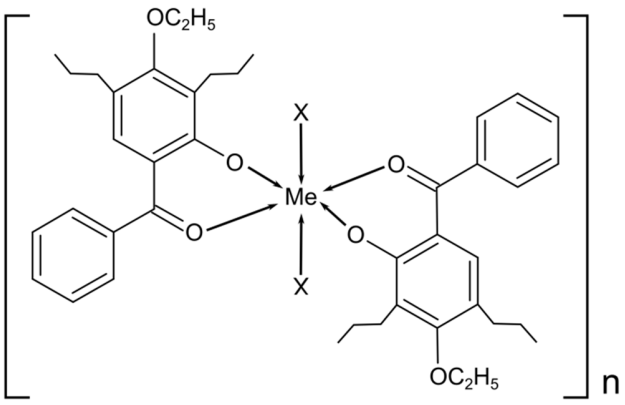


Figure 14. Proposed structure of the polychelate (Me = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III) X = H_2O) [29].

The polymeric L showed activity against the yeast strain while the polychelates showed significantly enhanced antibacterial activity against one or more bacterial species. All the polychelates had similar antimicrobial activities with a minimum concentration which inhibited the microbial growth of 500 ppm [29].

Ln complexes of bis(benzimidazole-2`-yl-methyl)amine (BImz) with molecular formula $[M(BImz)X_3 \cdot H_2O] \cdot nH_2O$ (M = La(III), Pr(III), Nd(III), or Gd(III); X = Cl or ClO_4 and n = 1, 2 or 3) were prepared by Siddiqi and collaborators [30]. The antimicrobial activity of the complexes was evaluated against the fungal strains *AN* and *PN* and also the bacteria G (-) (*PA)* and G (+) (*BC).* Their activities were compared with the activity of the standards *Grisofulvin* (against fungi) and *Norfloxacin* (against bacteria). The cup–plate method was used and the estimation of the antimicrobial activity by measuring the size of the inhibition zone formed around the wells in the plates.

The L (BImz) presented low activity against both fungi and bacteria, while the complexes presented low to moderate activity. Against *AN*, the complexes with ClO_4 showed enhanced

activity compared to the free L whereas the complexes with Cl showed activity comparable to that of the L. On the contrary, against *PN* only the Cl complex of Nd(III) showed enhanced activity while all the other complexes presented the same activity as the L. Against the bacteria *BC* (G (+)) the complexes exhibited moderately high activity whereas against the bacteria *PA* (G (-)) didn't exhibit any activity due to the higher lipid content in the cell membrane of *PA* compared to *BC* which prevents the diffusion of complex inside the cell. The increased activities of the complexes compared to the L are attributed to the synergistic effect that increases the lipophilicity of the complexes allowing their penetration into lipid membranes of organisms and thus facilitating the blockage of metal binding sites in enzymes [30].

In the study of Shebl et al. Ce(III) complexes with an organic L (H_3L, Figure 15) formed by the condensation of thiocarbohydrazide with 2-hydroxy-1-naphthaldehyde were described [31]. Also, ternary complexes were synthesized by using 1,10-phenanthroline or oxalic acid as a secondary L (Figure 16).

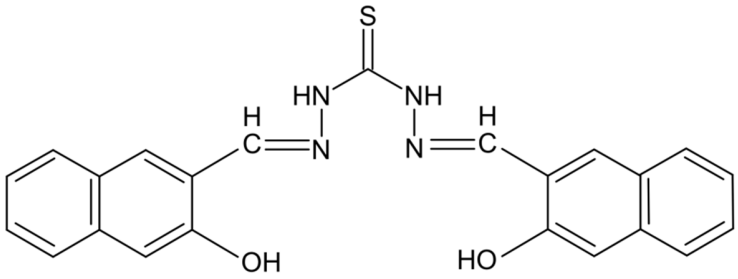


Figure 15. Structure of the H_3L L [31]

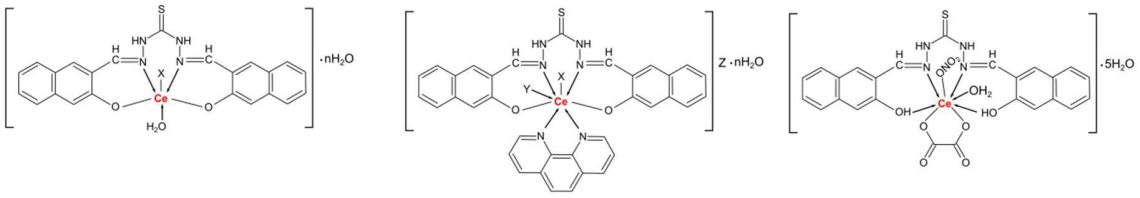


Figure 16. Representative structures of the binary complexes of the H_3L L (left); representative structures of the ternary complexes of the H_3L L that were prepared by using 1,10-phenanthroline as a secondary L (center) and oxalic acid as a secondary L (right) [31].

The antimicrobial activity of H_3L and its complexes was estimated against the G (+) bacteria (*SA*), G (-) bacteria (*EC)* and the fungi *CA* and *AF* and compared with the activity of *Tetracycline* (standard antibacterial) and *Amphotricine B* (standard antifungal). In all cases the Ce(III) complexes were more active than the H_3L, especially against *CA* for which the activity was comparable with the standard antifungal. For the other fungal strain *AF*, the complexes and L were inactive [31].

The synthesis and characterization of binary La(III) complex with sparfloxacin (HL_1) (Figure 17) ($[La(III)(L_1)_2{\cdot}NO_3{\cdot}H_2O]{\cdot}2H_2O$) and ternary La(III) complex with sparfloxacin (HL_1) (Figure 18 left) and DL-alanine (H_2L_2) ($[La(III)(L_1)(HL_2){\cdot}NO_3{\cdot}H_2O]{\cdot}H_2O$) (Figure 18 right) were reported by El-Gamel and collaborators [32]. The sparfloxacin (5-amino-1-cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-

difluoro-1,4-dihydro-4-oxo-3 quinoline carboxylic acid)) was chosen as L due to its well-known high activity against pathogens that cause urinary tract and respiratory infections [33].

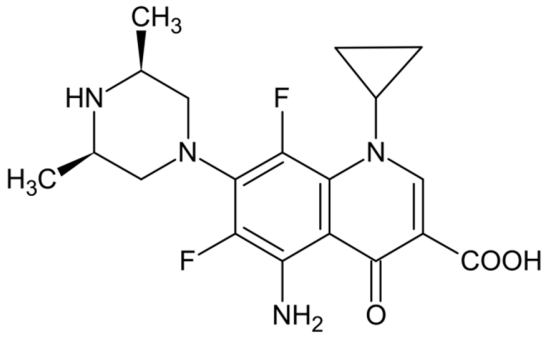


Figure 17. Structure of sparfloxacin (HL_1) [32].

The antimicrobial activity tests were carried out on G (+) (*SA*), G (–) (*EC*) bacterial species and *AF* and *CA* fungi using assay plates disc method.

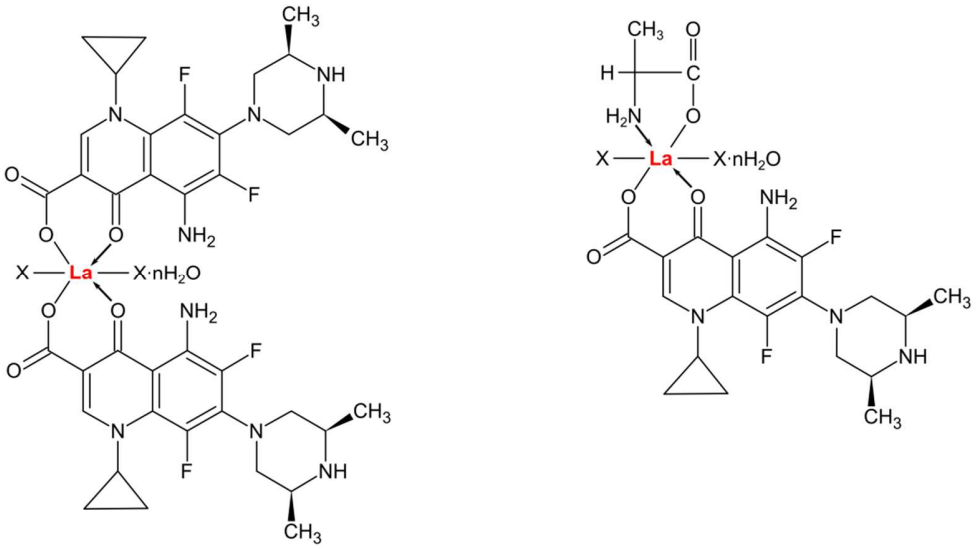


Figure 18. Structure of La(III) binary complex (left) and ternary complex (right) [32].

Against *SA* and *EC*, the free HL_1, La(III) binary and ternary complexes showed the same activity and their antibacterial effect was higher than the one of standard *Tetracycline*. These results indicate that complexes could be applied in the treatment of some diseases caused by *EC* like, Gastroenteritis, Septicaemia, Urinary tract infections [32]. On the contrary, when tested against fungi strains HL_1 and its La(III) binary and ternary complexes didn't present any activity compared to the standard *Amphoterician B*.

In the same year a new complex of moxifloxacin (MOX) with Ce(IV) ($[Ce(MOX)_2](SO_4)_2 \cdot 2H_2O$) was synthesized by Sadeek et al [34] and tested against three G (+) and three G (-) bacterial strains and compared with the reference drug *Moxifloxacin* (Figure 19). Moxifloxacin belongs to the fourth generation fluoroquinolone antibiotics used for the treatment of community and

hospital-acquired infections which is employed when all other antibiotics have failed. Moxifloxacin is bound to the Ce ion through the pyridone oxygen and one carboxylate oxygen acting as bidentate L.

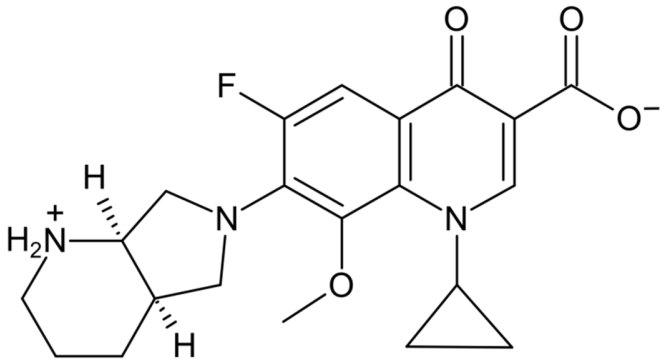


Figure 19. Structure of moxifloxacin [34].

The susceptibility of the tested bacterial strains towards moxifloxacin and its Ce(IV) complex (Figure 20) was determined by measuring the size of inhibition zone diameter.

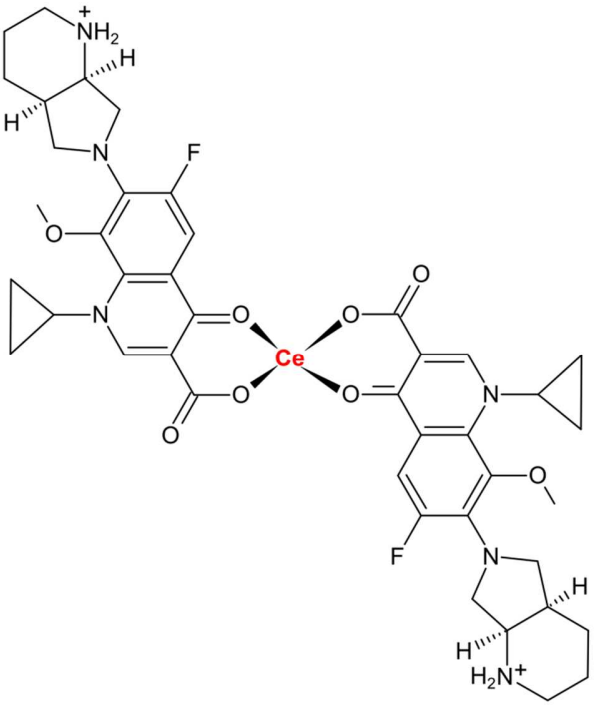


Figure 20. The coordination mode of Ce(IV) with moxifloxacin [34].

On one hand, the complex showed not significant activity against *EC* K32 and zero activity for *PA* SW1 and *KO* K4. On the other hand it showed significant activity against *BO* and it was highly active against *BS* and *SA* being more active than standard *Moxifloxacin* [34].

Jin and collaborators synthesized ternary complexes of Ln with 2,6-pyridine dicarboxylic acid and picolinic acid with general formula $[Ln(DPA)(L^{\alpha})(H_2O)]\cdot 2H_2O$ (Ln = Pr(III), Nd(III), Sm(III), Eu(III), Er(III); DPA = 2,6-pyridine dicarboxylic acid; HL^{α} =α-picolinic acid) (Figure 21) [35]. DPA and HL^{α} were chosen since they can inhibit the growth of bacteria due to the presence of several potential donors N, O [36].

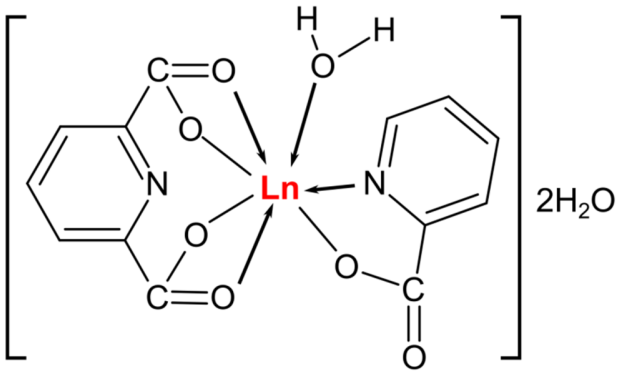


Figure 21. Proposed structure for the complexes (Ln = Pr(III), Nd(III), Sm(III), Eu(III), Er(III)) [35].

All the compounds were evaluated against G (-) (*EC* ATCC11229) and G (+) (*SA* ATCC6358P) bacterial strains employing the paper disc diffusion method. All the tested ternary complexes exhibit antibacterial activities against *EC* and *SA* with better activity compared to the free L, being $[Nd(DPA)(L^{\alpha})(H_2O)]\cdot 2H_2O$ the most active one with the diameter of growth inhibition area (17 and 15 mm) and the MIC (400 and 450 µg/mL) [35].

Refat et al. studied complexes form by *Norfloxacin* (norH) antibiotic drug with two Ln (La(III) and Ce(III)) metal ions prepared in normal and nano-structure [6]. The antimicrobial activity of the obtained complexes $[La(nor)_3]\cdot 3H_2O$ and $[Ce(nor)_3]\cdot 2H_2O$ (Figure 22) was evaluated against G (-) (*EC, PA),* G (+) *(SA, BS*) bacterial and fungal (*AF* and *CA*) strains using disc diffusion method.

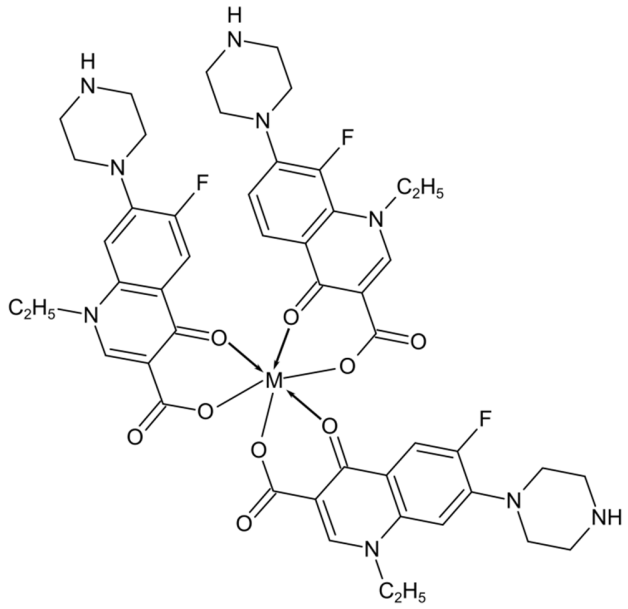


Figure 22. Proposed structure for $[M(nor)_3]xH_2O$ complex (M = La(III) or Ce(III)) [6].

The nano-particles complexes were more active than the free norH and normal Ln complexes against all organisms tested, with the exception of nanotype of Ce(III)/nor against *AF* fungus strain. When the inhibition zone diameter was considered as reference, nanotype La(III)/nor compound had the highest anti-microbial activity against all tested organisms. When comparing the activity of the Ln complexes with the antibacterial agent (*Tetracycline*) and antifungal agent (*Amphotericin B*), the nanotype La(III)/nor compound gained approximately 50 % more activity while the La(III)/nor and Ce(III)/nor compounds in normal types displayed only antibacterial activity with approximately 30 % of antibacterial agent activity. A possible explanation for the enhanced activity of the nanotype La(III)/nor compound was that the outer membranes of the target organisms (bacteria or fungus) were more permeable for the nanotype structures compared to the normal structures [6].

In the study of Zhao and collaborators several ternary complexes of Ln ions (La(III) Sm(III), Eu(III), Tb(III), Dy(III)) with benzoic acid and a neutral L 2,4,6-tri(2-pyridyl)-s-triazine (TPTZ) were synthesized and tested against G (-) (*EC)* bacteria employing filter paper disc diffusion method [37]. TPTZ was chosen as L due to its antimicrobial activity reported in previous studies by Patel et al. [38,39]. All studied Ln ternary complexes ($[Ln(C_6H_5COO)_3(TPTZ)]\cdot 4H_2O$) exhibited good antibacterial activity against *EC*, compared to the free L which presented weak antibacterial activity [37].

Aragón-Muriel and Polo-Cerón studied trivalent La complexes with 4-(R)-cinnamate (4-Rcinn, R = H (1), MeO (2), Cl (3)) and 4-methoxyphenylacetate L (4) (Figure 23) since both cinnamic acid and Ln complexes have shown biologic activity previously. Thus, their antifungal activity against *CA*, *AN* and *TM* were examined by determining MIC (mg/mL) [40].

The results indicated that all the complexes (1–4) were active against the tested strains. Complexes 1–3 showed antifungal activity against *TM* superior or comparable to those of cinnamic acid, while complexes 2 and 4 showed similar antifungal activity against *AN* and *CA*. As the activity of compounds 1 and 3 was comparable to the activity of cinnamic acid suggested that the chlorine substituent did not show any significant inhibitory activity against the tested strains. On the contrary, complex 2 containing a methoxy group with electron-donating effect presented better activity that the complexes 1–3, suggesting that the presence of donor systems in the L inhibited enzyme activity. The results obtained in this study showed that the change of the substituents on the aromatic ring (unsaturated hydrocarbon chain or methoxy group) produced significant differences in terms of antifungal activity [40].

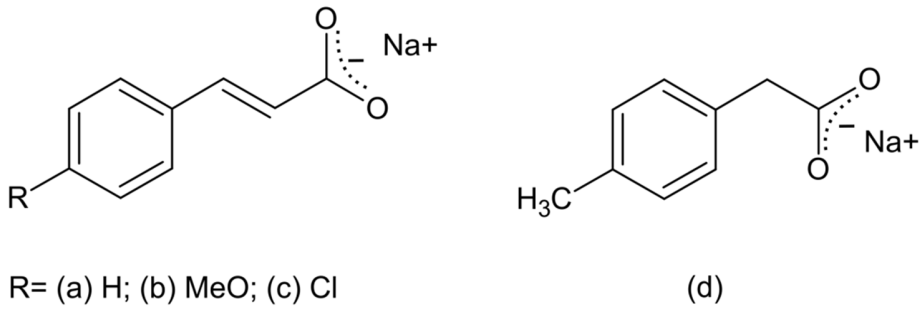


Figure 23. Structural formula of the sodium L precursors (NaL): (a) sodium cinnamate Na(cinn), (b) sodium 4-methoxycinnamate Na(4-MeOcinn), (c) sodium 4-chlorocinnamate Na(4-Clcinn), and (d) sodium 4-methoxyphenylacetate Na(4-MeOphac) [40].

A Dy(III) complex containing 1,10-phenanthroline (phen) $[Dy(phen)_2(OH_2)_3Cl]Cl_2{\cdot}H_2O$ (Figure 24) was synthesized by Khorasani-Motlagh and collaborators [41].

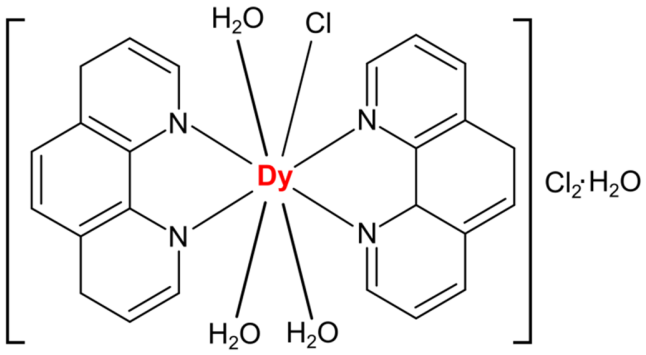


Figure 24. Structure of complex $[Dy(phen)_2Cl(OH_2)_3]Cl_2{\cdot}H_2O$ [41].

Its antibacterial effect was tested against G (+) bacteria (*ML, ENT, BAC* and *BAC C*) and G (-) bacteria (*SM, KP, EC, Shigella, AB* and *SP B, C)* using the disk diffusion method. For each experiment, the values of radius of the inhibition zone around each disk were determined. Dy(III) complex showed an efficient antibacterial activity against the bacteria tested [41].

In another study published by the same authors a similar complex $[Yb(phen)_2(OH_2)Cl_3](H_2O)_2$ (phen = 1,10-phenanthroline) was synthesized and tested against several G (+) (*ML, BAC, BAC C, ENT*) and G (-) (*SM, KP, EC, Shigella, AB,* and *SPB, C*) bacterial species by determining the MIC [42]. The Yb(III) complex had high antimicrobial activity with 6.9 mg/10 mL MIC for all the bacteria tested.

The same type of complex of Y(III) with 1,10-phenanthroline as L, $[Y(phen)_2Cl(OH_2)_3]Cl_2{\cdot}H_2O$ was prepared and tested against G (+) bacteria (*ML, BAC* and *BAC C*) and G (-) bacteria (*SM, KP, EC, Shigella, AB, ENT* and *SPB, C*) in a study published by the same authors [43]. The same results as in the case of Yb(III) complex [42] were obtained with a slight difference for the MIC values: for Y(III) the MIC was 6.3 mg/10 ml, while for Yb(III) complex the MIC value was 6.9 mg/10 mL.

Liu et al. synthesized Ln complexes with general formula $[Ln(3\text{-Br-5-IBA})_3phen]_2$ (Ln(III) = Er (1), Tb (2), Dy (3) and Ho (4); 3-Br-5-IBA = 3-bromo-5-iodobenzoate; phen = 1,10-phenanthroline) [44]. The antimicrobial activity of the free L and its Ln complexes against G (-) (*EC)* and G (+) *(SA*, *CA)* bacterial strains was tested employing the disc diffusion method by evaluating the diameter of growth inhibition area in mm. The L were considered inactive (diameter of 5 mm), while the complexes had a moderate antimicrobial effect against *CA* and *SA*, and a good antibacterial activity against *EC*. The authors conclude that the antimicrobial activity of the complexes is probably associated with disturbance of the functions related with cell division of fungi and bacteria such as cell wall, protein, and/or DNA biosynthesis [44].

In the study of Abbs Fen Reji et al. Ln complexes of Eu(III), Gd(III), Nd(III), Sm(III), and Tb(III) with phenylthioacetic acid (Figure 25) were synthesized and their antibacterial and antifungal properties were evaluated against the bacterial G (-) (*EC, PA)*, G (+) (*BS, SA*) and fungal (*AN, AF*, and *CA)* strains using disc diffusion method [45]. *Amikacin, Ofloxacin* and *Ciprofloxacin* were used as standards antibacterial agents and *Nystatin* as standard antifungal agent.

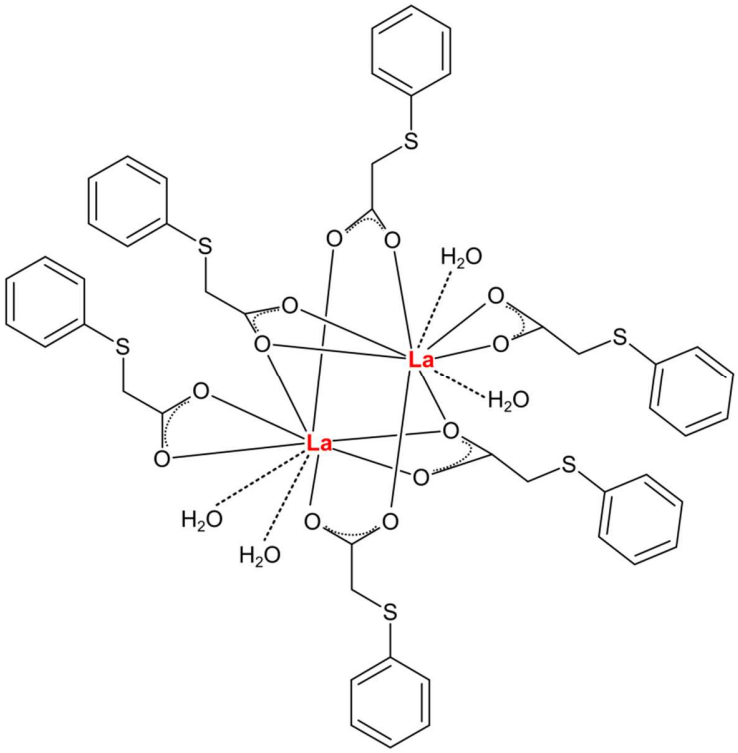


Figure 25. Proposed structure for Ln(III) complexes (Ln = Eu(III), Gd(III), Nd(III), Sm(III), and Tb(III)) [45].

The antimicrobial studies revealed that the Ln complexes showed higher activity compared to the free L. All the studied complexes exhibited moderate to strong antimicrobial activity, being more active against bacteria than the fungi. The Nd(III) complex exhibited the highest activity among the studied Ln complexes towards fungal species and also good antibacterial activity, especially against the G (+) bacteria (*EC* and *BS)* with the same or higher activity than the standard antibiotics. The Eu(III) and Gd(III) complexes exhibited moderate antibacterial activity [45].

In the same year a similar study was published by Shiju et al. in which Ln complexes of La(III), Pr(III), Nd(III), Sm(III) and Ho(III) with phenylthiopropionic acid were synthesized and their antimicrobial activity was tested against the bacterial and fungal species [46]. Though the L used in this study was slightly different from the one used by Abbs Fen Reji et al. [45], basically the same results were obtained. The Ln complexes were more active than the free L, being Nd(III) complex the most active.

Ln complexes of [1,2-bis(benzimidazole-2-yl)ethane dihydrochloride], $L^1$2HCl and [1,4-bis(benzimidazole-2-onium)butane dihydrochloride], $L^2$2HCl with molecular formulae $[Ln(L^1)_2Cl_3H_2O]$ and $[Ln(L^2)_2Cl_3H_2O]2H_2O$ (Ln (III) = La(III), Pr(III), Nd(III) and Gd(III)) were prepared and tested against G (-) (*PA*), G (+) (*BC*) bacteria and fungi (*AN* and *PN*) in the study of Siddiqi et al. [47]. The antimicrobial activities of the L and their Ln complexes were compared with the ones of *Greseofulvin* and *Norfloxacin*, used as standards for antibiotic and antifungal treatment. Both L were less active than the Ln complexes against the fungi and the bacteria. Against *AN*, all

complexes showed comparable activity to that of the s, though, against *PN*, enhanced activity compared to the L was observed for the complexes $[Nd(2L^1)Cl_3]\cdot H_2O$ and $[Nd(2L^2)Cl_3]\cdot 3H_2O$. Against G (+) bacteria the Ln complexes exhibited moderately high activities compared to the L, whereas against G (-) bacteria the complexes were inactive due to the higher lipid content in the cell membrane of G (-) compared to G (+) which prevents the diffusion of the complexes into the cell. Nevertheless, both L and the Ln complexes exhibited lower activity compared to the standard antibacterial and antifungal drugs [47].

In their study, Zheng and collaborators synthesized Ln complexes with a general formula $[Ln(3,5\text{-}DmeoxBA)_3(phen)]_2$ (Ln (III) = Tb(III), Dy(III), Er(III), Yb(III); 3,5-DmeoxBA = 3,5-dimethoxybenzoic acid; phen = 1,10-phenanthroline) and tested against bacteria G (-) (*EC)*, G(+) (*SA*) and fungus (*CA*) [48]. The results showed that all four complexes possessed good antimicrobial activities against bacteria and fungus, while the free L were inactive. The most active complexes against *EC* were Tb(III) and Dy(III) complexes whereas against *CA,* Er(III) and Yb(III) showed better activities [48].

In the article published by Andotra and collaborators, La(III) complexes with general formula $[La(ROCS_2)_3\cdot nL]$ (where n = 2, L = NC_5H_5 or $P(C_6H_5)_3$ and n = 1, L = $N_2C_{12}H_8$ or $N_2C_{10}H_8$); R = o-, m-, p-$CH_3C_6H_4$ and $C_6H_5CH_2$) (Figure 26) were prepared and tested against fungus *FO* [49].

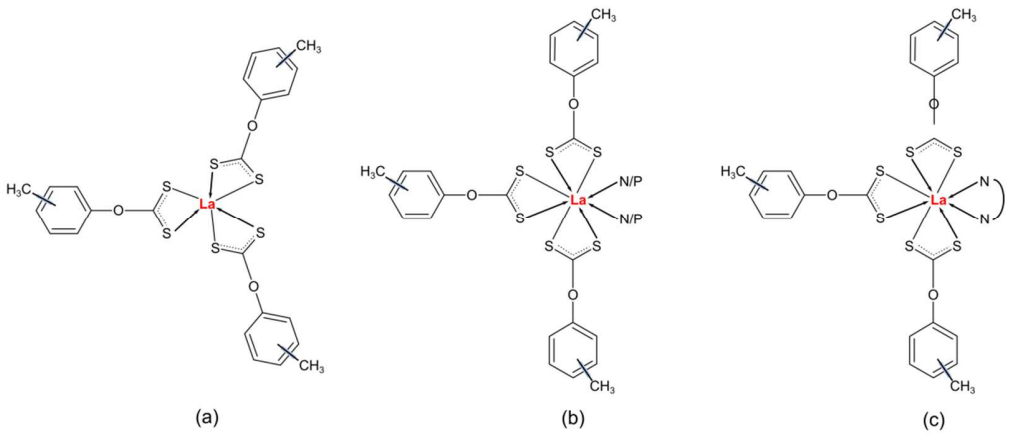


Figure 26. (a) Proposed hexacoordinate structure for [La(o-, m- and p-$CH_3C_6H_4OCS_2)_3$]; (b) Proposed octacoordinate structure for [La(o-,m- and p-$CH_3C_6H_4OCS_2)_3$ 2N/P]; [N=NC_5H_5 and P=$P(C_6H_5)_3$; (c) Proposed octacoordinate structure for [La(o-, m- and p-$CH_3C_6H_4OCS_2)_3\cdot N_2C_{12}H_8/N_2C_{10}H_8$] [49].

The results showed that the complexes were more active than the free L inhibiting the growth of fungus significantly. Antibacterial activity was studied against two bacterial strains G (-) (*KP)* and G (+) (*BAC C)* and compared with the activity of *Penicillin* as standard antibacterial agent. The free L were inactive against the bacterial strains but La complexes showed activity though lower than the *Penicillin*. However, the complex $[La(C_6H_4CH_2OCS_2)_3{\cdot}N_2C_{12}H_8]$ showed better activity against *KP* and *BAC C* than reference drug *Penicillin*.

The synthesis of Ln(III) complexes (Ln (III) = La(III), Ce(III), Pr(III), Nd(III), Sm(III)) of 4-butyl-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione (OPB) (Figure 27) was reported by Binil et al. [50].

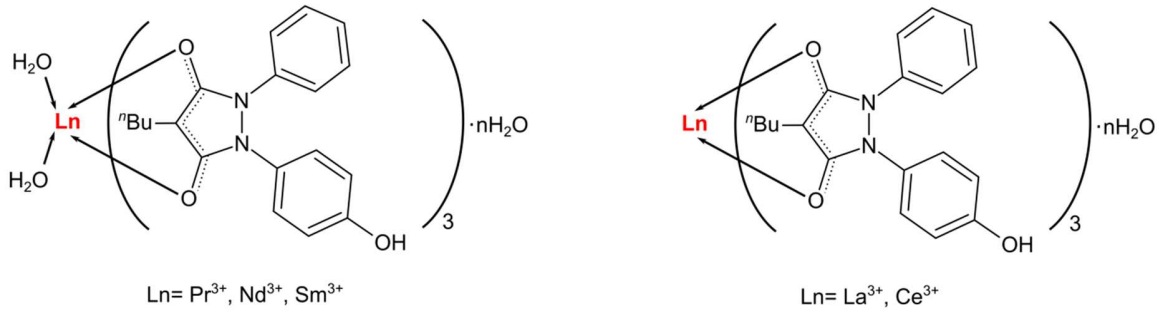


Figure 27. Proposed structure of Ln(III) complexes with OPB [50].

The complexes were tested against bacteria G (+) (*SA* (MTCC-96), *BAC C* (MTCC-430), *PC*), G (-) (*EC* (MTCC-433), *ST* (MTCC- 733), *VC* (MTCC-3906)) and fungi (AF*, AN, CA* (MTCC-183)) employing agar disc diffusion method. The size of the inhibition zone formed around the paper discs was measured in mm. The free L was not active while the complexes showed less to moderate activity, with some exceptions: (i) $[La(OPB)_3]{\cdot}6H_2O$ was inactive against *AF, CA* and *PC*; (ii) $[Ce(OPB)_3]{\cdot}5H_2O$ was inactive against *VC;* (iii) $[Pr(OPB)_3(H_2O)_2]{\cdot}6H_2O$ was inactive against *ST*; (iv) $[Nd(OPB)_3(H_2O)_2]{\cdot}4H_2O$ was inactive against *CA* and *PC*; and (v) $[Sm(OPB)_3(H2O)_2]{\cdot}6H_2O$ was inactive against *PC* [50].

Chandra and Agrawal synthesized complexes of Ce(III), Nd(III), Sm(III) and Eu(III) with NO-donor macrocyclic L (3,5,13,15,21,22-hexaaza-2,6,12,16-tetramethyl-4,14-dithiatricyclo[15.3.1.1(7-11)]docosane-1(21),2,5,-7,9,11(22),12,15,17,19-decaene) (Figure 28) [51]. Their antifungal capacity was determined against two plant pathogenic fungi (*AN* and *FO*) using poison food technique and employing *Captan* as standard fungicide.

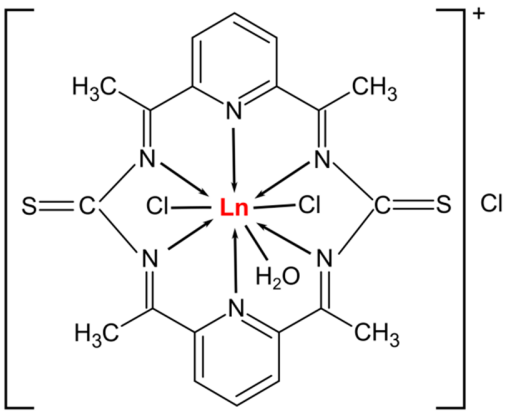


Figure 28. Proposed structure of the complexes [Ln = Ce(III), Nd(III), Sm(III) and Eu(III)] [51].

The free L doesn't exhibit any antifungal activity, but all Ln complexes exhibit good activities being $[Nd(L)Cl_2 \cdot H_2O]Cl$ the most active against *AN* while $[Sm(L)Cl_2 \cdot H_2O]Cl$ was found to be more active against *FO* [51].

Complexes of Sm(III) and Tb(III) with 2-aminobenzoic acid (anthranilic acid, AA) and 2-amino-5- chlorobenzoic acid (5-chloroanthranilic acid, AACl) (Figure 29) were synthesized by Essawy et al. [52]. The antimicrobial properties of the free Ls and their complexes were tested against G (+) bacteria (*SA*), G (-) bacteria (*EC*) and fungi (*AF* and *AN*) employing the standard disc agar diffusion method. Their antimicrobial activity was compared with the activity of *Tetracycline* (antibacterial agent) and *Amphotericin B* (antifungal agent). All the synthesized complexes were inactive against *AF* fungus, however they exhibit activity against *CA* fungus except $Tb(AA)_3$ which showed no activity against this type of fungi.

Almost all Ln complexes showed increased activity against *SA* (G (+) and *EC* (G (-)) bacteria in comparison with the free L AA and AACl. Moreover, AACl and their Sm(III) and Tb(III) complexes exhibited relatively increased activity compared with AA and $Ln(AA)_3$ equivalents [52].

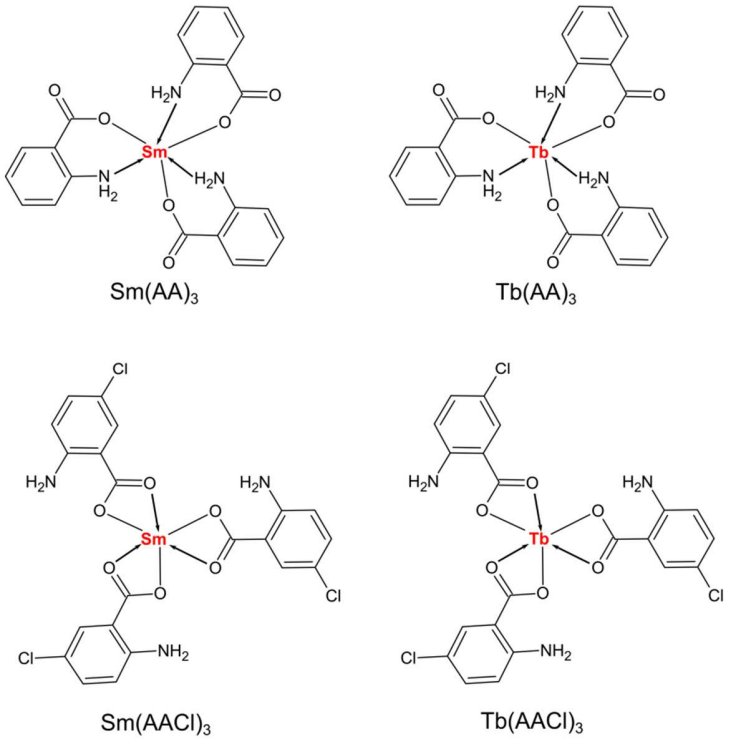


Figure 29. The proposed structures of: (a) Sm and Tb anthranilate complexes and (b) chloroanthranilate complexes [52].

The synthesis of Ln complexes of pyridoxine mono hydrochloride (vitamin B6) (Figure 30) with La(III), Ce(III), Sm(III) and Y(III) was reported by Refat et al. [53].

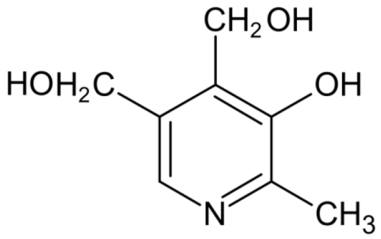


Figure 30. Structure of Pyridoxine (PN) L [53].

The antimicrobial properties of PN L and its Ln complexes (Figure 31) was determined against G (+) bacteria (*SA, BS),* G (-) bacteria *(EC, PA*) and two fungal species (*AF* and *CA*) employing filter paper disc method.

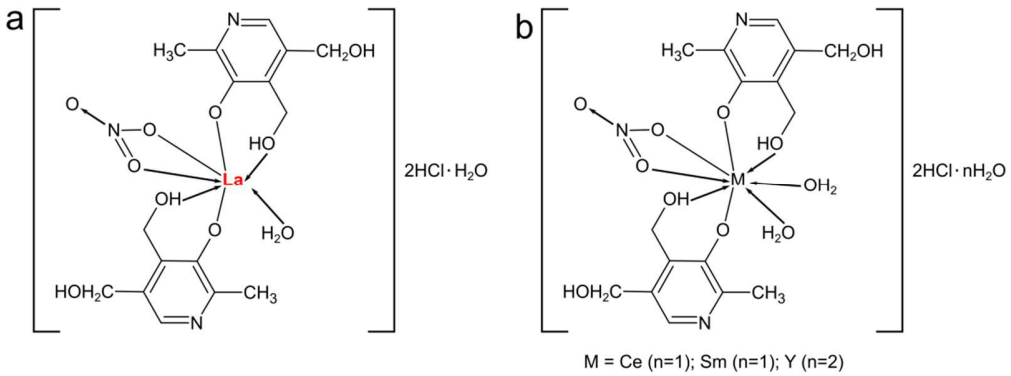


Figure 31. (a) Suggested chelating structure of pyridoxine HCl complexes with La(III) ion; (b) Suggested chelating structure of pyridoxine HCl complexes with Ce(III), Sm(III) and Y(III) ions [53].

The antimicrobial activity results of both free L and their Ln complexes showed that the compounds had both antibacterial and antifungal activity though they presented moderate activity compared to the one of standards *Tetracycline* (antibacterial agent) and *Amphotericin B* (antifungal agent). For all the tested microorganisms the Ln complexes order of activity was: Y(III) > Sm(III) > La(III) = Ce(III). Upon complexation with Ln, the L lost activity except in the case of Y(III) when it was enhanced against G (+) bacteria and fungi but it didn't affect the activity against G (-) bacteria. Generally, the antibacterial activity of the complexes was stronger than the antifungal activity [53].

The same authors published another article dealing with the synthesis of La(III), Ce(III), Sm(III) and Y(III) complexes of Enalapril maleate (Figure 32 and Figure 33) hypertensive drug and their antimicrobial activity against G (-) bacteria (*EC, PA*), G (+) bacteria (*SA, BS)* and fungi (*AF* and *CA*) using filter paper disc method [54]. Enalapril and its Ln complexes showed no activity against fungi and against the studied bacteria Enalapril was more effective than its Ln complexes except for the Sm(III) complex which showed slightly enhanced activity against *BS* compared to the free Enalapril. Among the Ln complexes, the most efficient was Y(III) complex except against *BS* against which Sm(III) was more active [54].

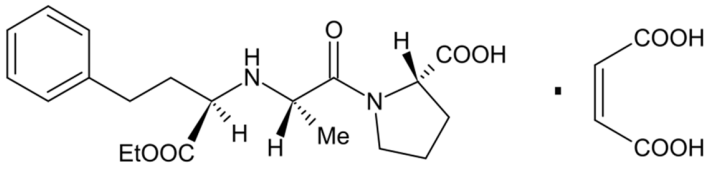


Figure 32. Structure of Enalapril maleat (Enal) L [54].

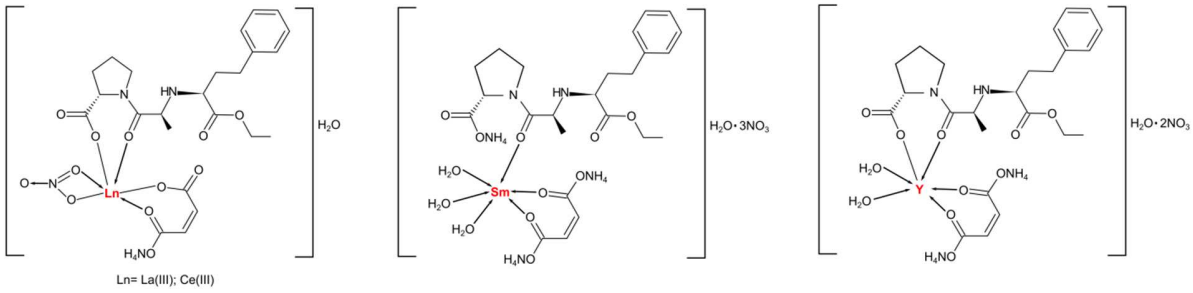


Figure 33. Suggested chelating structure of Enalapril complexes with La(III) and Ce(III), Sm(III) and Y(III) metal ions [54].

In the study of Subhan et al. mixed Ln complexes of Phendione and β-diketones have been synthesized, specifically [Eu(TFN)$_3$(Phendione)] (TFN = 4,4,4-trifluoro-1(2-napthyl)-1,3-butanedione), [Eu(HFT)$_3$(Phendione)] (HFT = 4,4,5,5,6,6,6-heptafluoro-1-(2-thienyl)-1,3-hexanedione), [Yb(HFA)$_3$(Phendione)] (HFA = hexafluoroacetylacetonate) [55]. Their antimicrobial activities were determined against G (-) (*EC, PP*) and G (+) (*SA*) using the disc diffusion method. The author's interest in the phendione was due to its biological activity and good chelating properties, being able to form monomeric and polymeric coordination complexes. Moreover, because of the redox properties of its free quinoid functional group phendione is able to cause the bacterial cell breaking and by binding to the protein synthesizing enzyme can inhibit protein synthesis for bacterial propagation [55]. The results showed that phendione and its Eu(III) and Yb(III) complexes exhibited significant antibacterial activities, being most active against *PP*.

Refat et al. synthesized Ln complexes (Ln = Ce(III), Sm(III) and Y (III)) of *Metformin* hydrochloride (Figure 34), and tested their antimicrobial properties against bacteria G (+) (*SA, BS*), G(-) (*EC,PA*) and two fungal species (*AF* and *CA*) using filter paper disc method [56].

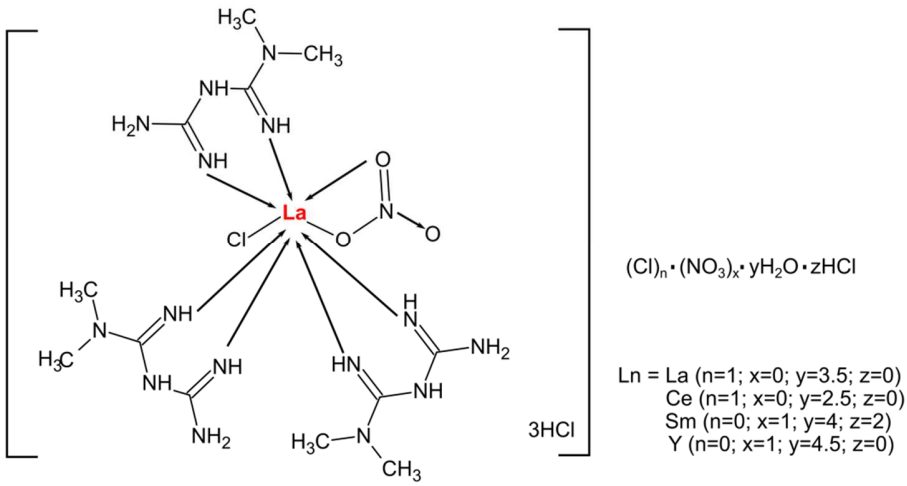


Figure 34. Proposed structure for chelating of Metformin HCl complexes with Ln metal ions [56].

The results indicate that the free L was not active but upon complexation with Ln(III) showed significant activity, in some cases comparable with the activity of *Tetracyclin* (standard antibacterial agent) and *Amphotericin B* (standard antifungal agent). The Ln complexes presented both antibacterial and antifungal activity, the most efficient complexes being: (i) La(III) against G (+) *SA*; (ii) Sm(III) against G (-) *PA* and fungus *AF* and *CA* and (iii) Y(III) against G (-) *EC* and *BS* [56].

In the study of Zhang et al., Ln complexes with the general formula $[Ln(3,4\text{-}DClBA)_3phen]_2$ (Ln (III) = Ho(III), Nd(III), Sm(III), Dy(III), Eu(III), Tb(III), Yb(III) and Er(III), 3,4-DClBA = 3,4-dichlorobenzoate, phen = 1,10- phenanthroline) were prepared [57]. Their antimicrobial activity was determined against G (-) (*EC*), G (+) (*SA*) bacterial strains and *CA* fungus using the filter paper disc diffusion method. Though the L had no inhibiting effect, its Ln complexes had antimicrobial activity toward all the studied microorganisms, the diameter of inhibition zone increasing with the increase of concentration. The most efficient were the Nd(III) and Sm(III) complexes with diameters of inhibition ranging from 12.29 to 33.95 mm. All complexes were more active against *CA* compared to the other microorganisms [57].

Poona et al. prepared ternary Tb(III) complexes $[Tb(HDAP)_3 \cdot biq]$, $[Tb(HDAP)_3 \cdot dmph]$ and $[Tb(HDAP)_3 \cdot bathophen]$ (Figure 35) using methoxy substituted hydroxyketone L HDAP (2-hydroxy-4,6-dimethoxyace tophenone) and an ancillary L 2,2-biquinoline or 5,6-dimethyl-1,10-phenanthroline or bathophenanthroline as L [58]. Their antibacterial activities against G (+) *(SA* (MTCC 3160)*, BS* (MTCC 441))*,* G (-) (*EC* (MTCC 443)) bacteria and antifungal activities against *CA* and *AN* were tested and compared with the activities of *Ciprofloxacin* (antibacterial agent) and *Fluconazole* (antifungal agent).

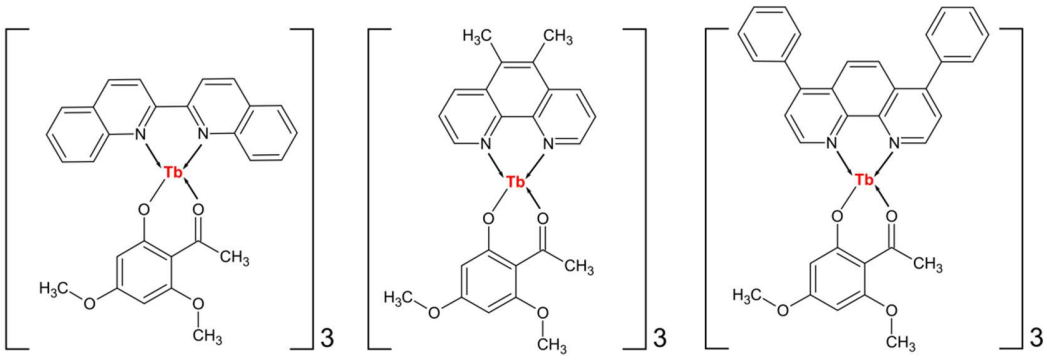


Figure 35. Proposed structures for Tb(HDAP)$_3$·biq (left), Tb(HDAP)$_3$·dmph (center), Tb(HDAP)$_3$·bathophen (right) [58].

The results showed that the HDAP had insignificant antimicrobial activity, while its Tb(III) complexes exhibited growth inhibition. Against *SA* all three Tb(III) complexes presented better activity than the standard drug and against *EC* only the Tb(HDAP)$_3$·bathophen complex was more active than the standard drug. Against fungi *CA* and *AN,* the same complex Tb(HDAP)$_3$·bathophen was most active, thus the authors concluded that this complex is a potent antimicrobial agent [58].

Continuing their work in preparation of Ln(III) complexes with 1,10-phenanthroline, Khorasani-Motlagh et al. report the synthesis of Eu complex with formula [Eu(phen)$_2$(OH$_2$)$_2$(Cl)$_2$](Cl)(H$_2$O) (phen = 1,10-phenanthroline) [59]. The complex's antibacterial activity was evaluated against two G (-) bacteria (*EC (*ATCC 25922) and *PA* (ATCC 27853)) and two G (+) bacteria (*SA* (ATCC 25923) and *EF* (ATCC 11700)) by determination of the MIC. The complex's activity was compared to the one of *Gentamycin* (G (-) antibacterial agent) and *Amikacin* (G (+) antibacterial agent).

The Eu(III) complex possessed an acceptable antibacterial activity in comparison with standard antibacterial agents that can be related to the presence of the Phen rings as a chelating L. The complex's MIC values against all strains were rather high, nevertheless the diameter of inhibition zones that the Eu(III) complex created were comparable to the ones created by the standard antibacterial agents and even higher in the case of *EF* and *SA.*

The same authors published another article regarding the screening of La(III) complex with 1,10-phenanthroline (phen), [La(phen)$_3$Cl$_3$·OH$_2$] against G (+) bacteria (*ML, BAC C* and *BAC*) and G (-) bacteria (*SM, Shigella, AB, KP, SPC, SPB, EC* and *ENT*) employing disc diffusion method and measuring the diameter of inhibition zone [60]. The results indicated that the La(III) complex was active only against G (-) bacteria such as *KP* (10 mm), *EC* (8 mm), *SPC* (8 mm) and *ENT* (7 mm).

In the study of Shafiy and Shebl a complex of Ce(III) (Figure 36) with quinolinone L (1-ethyl-4-hydroxy-3-(nitroacetyl)quinolin-2(1H)-one (H$_2$L)) was synthesized and tested against G (+) (*SA*), G (-) (*KP, EC, PV*) bacterial strains and *CA* fungus by determining the MIC values [61].

The complex showed low activity against all organisms (MIC > 50 μg/mL) when compared with standard antibacterial (*Doxymicin*) and antifungal agents (*Fluconazole*) with MICs ranging from 5 to 10 μg/mL.

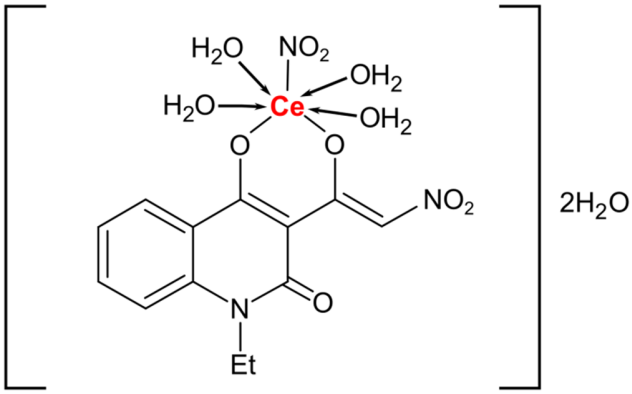


Figure 36. Proposed structures of Ce(III) complexe with the quinolinone L [61].

Shahid et al. synthesized eight complexes of Ln chlorides and perchlorates (Ln = La(III), Pr(III), Nd(III) and Gd(III)) with the L^2 (H_2L = 2,2'-iminobis [N-(3-hydroxypropyl)acetamide]) (Figure 37) with general formulae $[LnLCl(H_2O)_2]\cdot 2H_2O$ and $[LnLClO_4(H_2O)_2]\cdot H_2O$ [62]. Their antimicrobial activity was tested against G (+) (*SA, BS)* bacteria and fungal strains *CA* and *PM* and compared to the activity of *Greseofulvin* and *Norfloxacin*, standard agents used against fungi and bacteria by measuring the size of the inhibition zone.

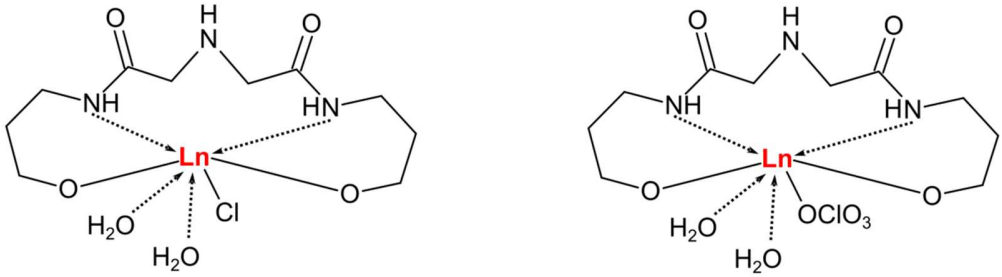


Figure 37. Proposed structure for $[LnLCl(H_2O)_2]\cdot 2H_2O$ (left) and $[LnLClO_4(H_2O)_2]\cdot H_2O$ (right) complexes [62].

In case of *CA*, the complexes $[LnLClO_4(H_2O)_2]\cdot H_2O$ of Nd(III) and Gd(III)) showed increased activity compared to the L whereas the complexes $[LnLCl(H_2O)_2]\cdot 2H_2O$ exhibited activity comparable to that of the H_2L. All the complexes exhibited comparable activity with *Greseafulvin* but lesser activity than *Norfloxacin*. In the case of *PM*, increased activity compared to the L was observed for the complex $[LnLCl(H_2O)_2]\cdot 2H_2O$ of Nd(III) and Gd(III)) only, which was higher than the activity of *Greseaofulvin* but lower than one of *Norfloxacin* standard.

Against the bacteria *BS* the complexes exhibited moderately high activities compared to the L except complex $[LaLClO_4(H_2O)_2]\cdot H_2O$ which showed moderate activity. These complexes showed better activity than *Norfloxacin* but lower activity than *Greseofulvin*. Nonetheless, against bacteria *SA* the complexes didn't show any activity compared to the L.

The study of Zapała et al. described the synthesis of binuclear binary and ternary complexes of Sm(III), Eu(III), and Gd(III) ions with N-phenylanthranilic acid and 1,10-phenanthroline with

general formulas $Ln_2(C_{13}H_{10}NO_2)_4(OH)_2 \cdot 4.5H_2O$ and $Ln_2(C_{13}H_{10}NO_2)_4(phen)(OH)_2 \cdot H_2O$ [63]. Their antibacterial properties against G (-) (*EC* (ATCC 10538), *PA (*ATCC 15442)) and G (+) (*SA (*ATTCC 6538)) bacterial strains were evaluated by the determination of MIC (μg /mL). N-phenylanthranilic acid and the binary complexes presented similar activity against G (-) bacterial strains with MIC = 0.250 μg / mL.

Phenanthroline was introduced into the complexes structure since it is known to have antibacterial activity and it was expected that its presence will increase the complexes antibacterial activity. The obtained results showed that the phenanthroline MIC was 0.0625 μg/mL against *EC* and 0.250 μg/mL and *PA*. Consequently, the ternary complexes presented enhanced activity against *EC*, especially the Gd(III) complex (MIC = 0.0625 μg/mL) in comparison with the binary ones. On the contrary, against *PA* the ternary and binary complexes had the same activity (MIC = 0.250 μg/mL).

MIC values of N-phenylanthranilic acid and the Sm(III) complex against *SA* were 0.250 μg/mL while amongst the binary complexes the Eu(III) complex exhibited the highest activity (MIC = 0.125 μg/mL) and the Gd(III) complex the lowest one (MIC = 0.500 μg/mL). The enhanced activity of binary complexes compared to the ternary ones, was attributed to the increased lipophilic character which allowed their permeation through lipid layers of the bacterial membrane. It is important to mention that the antibacterial activity of the synthesized compounds with respect to *PA* is comparable to *Tetracycline* and greater than the activity of *Kanamycin, Erythromycin*, and *Ampicillin* employed as standard antibacterial agents [63].

Ln complexes with Schiff bases

This section reflects the contribution of Schiff bases to the design and development of new Ln complexes with potential biological activities with fewer side effects. The results are summarized in Table 2.

Table 2. Examples of Ln(III)-Schiff bases complexes and their antimicrobial activity.

Ln(III)- Schiff bases Complexes		**Antimicrobial activity tested**			**Ref.**
Ln(III)	**Schiff bases (L)**	**G (+)**	**G (-)**	**Fungi**	
Ce(III)	bis-salicylatothiosemicarbazide	-	-	*AF, PI, SR, AA,CA*	[67]
La(III)	8-formyl-7-hydroxy-4-methylcoumarin and o-phenylenediamine/ethylenediamine	*SA*	*PA, EC, ST*	*AN, AF and Cladosporium*	[69]
Nd(III), Dy(III), Sm(III), Pr(III), Gd(III), Tb(III), La(III), Er(III)	N,N'-bis(1-naphthaldimine)-o-phenylenediamine	*SA*	*SD, PA, EC, PV, Klebsiella, Serratia*	-	[70]

Nd(III), Dy(III), Sm(III), Pr(III), Gd(III), Tb(III), La(III), Er(III)	N,N'-bis(1-naphthaldimine)-o-phenylenediamine	*SA, Spy, EF*	*EC, KP, PrM, SE, PA*	-	[71]
Nd(III), Dy(III), Sm(III), Pr(III), Gd(III), Tb(III), La(III), Er(III)	N,N'-bis(2-hydroxynaphthylmethyli-dene)-1,3-propanediamine	*Spy, SA, EF*	*PV, PA, SD, Klebsiella, Serratia*	-	[72]
La(III), Ce(IV)	[N-(2-hydroxybenzyl)-L-methionine acid]	*SA*	*EC*	*AF, CA*	[73]
Dy(III), Sm(III), Pr(III), Nd(III), La(III), Er(III), Gd(III)	(N, N'-bis (1-naphthaldimine)-o-phenylenediamine)	*SA*	*SD, PV, PA, EC, SM, KP*	-	[74]
Pr(III), Sm(III), Gd(III), Tb(III), Er(III), Yb(III)	2-[(5-bromo-2-hydroxy-benzylidene)-amino]-3-hydroxypropionic acid	*SA*	*EC, PV, PA*	-	[75]
La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Yb(III)	2-aminopyrimidine condensed with 2-hydroxyacetophenone	*EC, ST*	*BM, SA*	-	[76]
La(III)	(E)-3-((2-hydroxynaphthalen-1-yl) methyleneamino)-2-methylquinazoline-4(3H)-one	*MRSA*	-	-	[77]
Nd(III), Sm(III)	condensation of 3-(phenyl/substitutedphenyl)-4-amino-5-mercapto-1,2,4-triazole with diacetyl/benzil	*BS, SA*	-	*AN, CV, CC*	[78]
La(III), Sm(III)	2-[(pyridin-2-ylmethylidene)amino]-6-aminopyridine	*SA*	*EC*	-	[79]
La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III), Er(III)	[2-thiophenecarboxylic acid, 2-(2-pyridinylmethylene)hydrazide]	*SA, Spy, EF*	*EC, KP, PrM, SE, PA*	-	[80]

Ce(III)	2-(2,3-dihydro-1H-indolo[2,3-b]phenazin-4(5H)ylidene)hydrazinecarbothio amide , 3-(ethoxymethylene)- 2,3-dihydro-1H-indolo[2,3-b]phenazin-4(5H)-ylidene)hydrazinecarbothioamide , (Z)-3-benzylidene-2,3-dihydro-1H-indolo[2,3-b]phenazin-4(5H)ylidene)hydrazine carbothioamide	*BS (ATCC 6633), SA (ATCC 6538P*	*EC (ATCC 25922)*	*CT (ATCC 13803), AN (MTCC 282)*	[7]
La (III), Ce (III), Pr (III), Nd (III), Sm (III), Eu(III), Gd(III)	2-[N-(20-hydroxy-1-naphthylidene)amino]-3-carboxyethyl-4,5-dimethylthiophene	*SA, BS*	*EC, PA*	*AN, CA*	[81]
Eu(III), Gd(III), Nd(III), Sm(III), Tb(III)	derived from glycylglycine and 4-nitrobenzaldehyde	*BS, SA*	*EC, PA*	*AN, AF, CA*	[82]
Er(III), Pr(III), Yb(III)	N^2,N^3-bis (anthracen-9-ylmethylene) pyridine-3,4-diamine	*BS, SA*	*EC, PA*	-	[83]

In the continuous search for designing new organic L supramolecular architectures, Schiff bases have been extensively studied due to their characteristic properties, such as thermal stability, relevant biological properties, high synthesis flexibility and medicinal utility [7]. Schiff bases (Figure 38) named after Hugo Schiff who first reported this type of structure in 1864, are compounds that contain azomethine group ($-RC = N -$) and are typically formed by the condensation of a primary amine with a carbonyl compound [64].

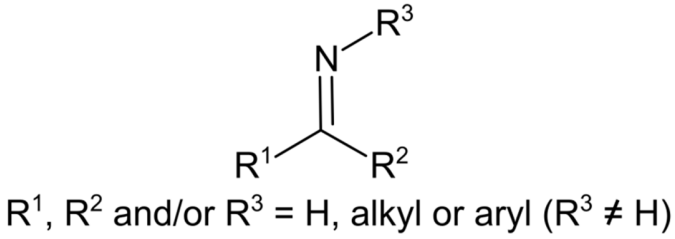


Figure 38. General structure of Schiff base [65].

Due to the presence in their structure of the imine group which gives them biological activities [66], the Schiff bases have been extensively explored for the development of new

bioactive substances, including antibacterial and antifungal agents. The antimicrobial activity might be related the presence of nitrogen atom of azomethine group which may form hydrogen bonds with the active centers of cell constituents and consequently interfere in normal cell processes [66].

El-Wahab and collaborators synthesized Ce(III) complex with the Schiff base H_2L, bis-salicylatothiosemicarbazide (Figure 39) in presence of different molar ratios of $LiOH·H_2O$ as a deprotonating agent [67].

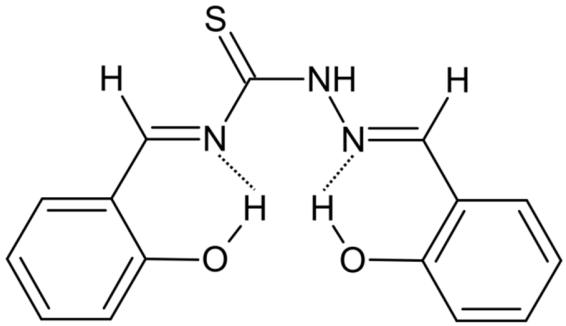
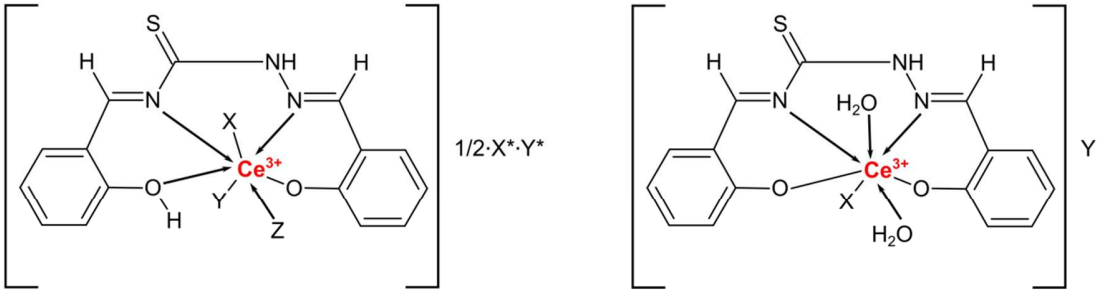


Figure 39. Bis-salicylatothiosemicarbazide Schiff base L (H_2L) [67].

The antimicrobial activity of these complexes (Figure 40) was evaluated against several bacterial species G (+) (*SA, BS),* G (-) (*PA, EC*) and five types of fungi (*AF, PI, SR, AA* and *CA*) using *Chloroamphinicol* as a standard antibacterial agent and *Terbinafin* as antifungal agent.

The antibacterial results showed that binary metal complexes $[CeHL(NO_3)_2(OH_2)]·(1/2)H_2O$ (molar ratio $Ce:H_2L:LiOH = 1:1:1$) and $[CeL(NO_3)(OH_2)_2]·H_2O$ (molar ratio $Ce:H_2L:LiOH = 1:1:2$) showed better activity than the free Schiff base L against G (+) bacteria *SA* but lower activity when tested against G (-) bacteria *BS, PA* and *EC*. The metal complexes showed better activity compared to free Schiff base L due to chelation which increases lipophilic nature of the central atom and favors its permeation through the cell membrane [68]. When compared between each other, the $[CeL(NO_3)(OH_2)_2]·H_2O$ complex exhibited better activity than $[CeHL(NO_3)_2(OH_2)]·(1/2)H_2O$.



X=Cl; $Y=H_2O$; $Z=X^*=Y^*=nil$;
$X=Y=NO_3$; $Y=X^*=H_2O$; $Y^*=nil$;
$X=Y=X^*=H_2O$; Z=nil; $Y^*=NO_3$;

X=nil; $Y=4H_2O$;
$X=NO_3$; $Y=H_2O$;
X=Y=nil;

Figure 40. Suggested structures of the binary complexes containing HL as monoanionic tetradentate L (left) and L as dianionic tetradentate L (right) [67].

The free Schiff base L was more active than Ce complexes against all type of fungi except *CA* for which $[CeHL(NO_3)_2(OH_2)]\cdot(1/2)H_2O$ complex showed similar activity. In this case, $[CeHL(NO_3)_2(OH_2)]\cdot(1/2)H_2O$ shows better antifungal activity compared with $[CeL(NO_3)(OH_2)_2]\cdot H_2O$ though both Ce complexes showed only moderate activity [67].

In the study of Kulkarni et al. a La(III) complex with Schiff bases derived from 8-formyl-7-hydroxy-4-methylcoumarin and o-phenylenediamine/ethylenediamine (Figure 41) was synthesized and its antibacterial G (+) (*SA),* G (-) (*PA, EC, ST*) and antifungal activity (*AN*, *AF* and *Cladosporium*) was determined by measuring the diameter of the zone showing complete inhibition [69]. Standard antibacterial (*Gentamycine*) antifungal drugs (*Fluconazole*) were also screened under similar conditions for comparison.

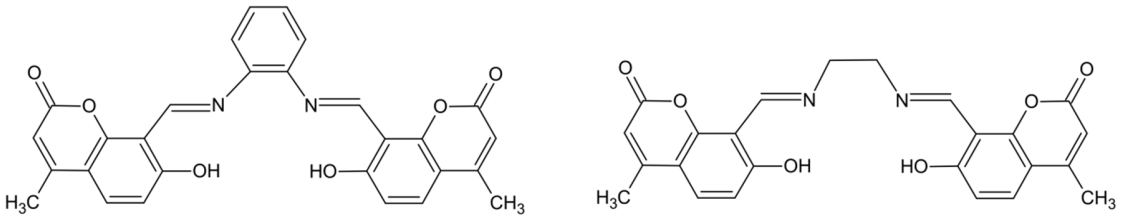


Figure 41. Structure of synthesized of Schiff bases H_2L^{I} (left) and H_2L^{II} (right) [20].

In the antibacterial studies, both the Schiff bases were found to be potentially active against *EC* and *ST*, while the La(III) complexes ($[La(H_2L^{I})(NO_3)]\cdot H_2O$ and $[La(H_2L^{II})(NO_3)]\cdot H_2O$) (Figure 42) shown much enhanced activity against *EC, PA* and *ST.* Furthermore, the complexes showed almost similar activity as that of standard drug (*Gentamycine*). Against the bacterial strain *SA*, both Schiff bases and their La(III) complexes showed higher activity compared to standard drug, although the antibacterial activity is all cases was low.

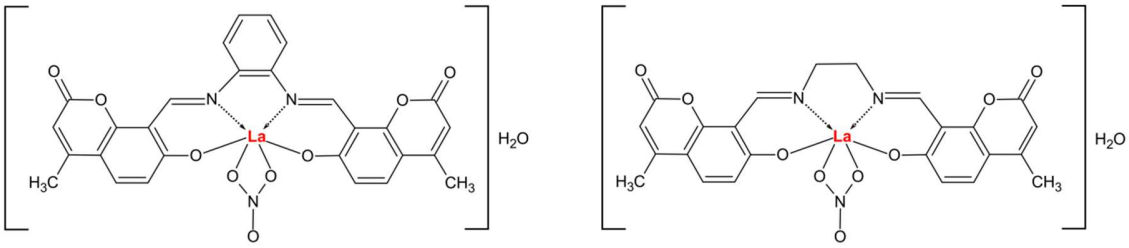


Figure 42. Proposed structures of $([La(H_2L^{I})(NO_3)]\cdot H_2O$ (left) and $[La(H_2L^{II})(NO_3)]\cdot H_2O$ (right) complexes [69].

Regarding the antifungal activity, both Schiff bases and their La(III) complexes showed almost the same activity as the standard drug *Flucanozole*. When compared the antibacterial and antifungal activities, the Schiff bases and their La(III) complexes showed enhanced antifungal activity.

The MIC was also determined and it varied from 10–24 µg/mL. Both Schiff bases were the most active in inhibiting the growth of the tested organisms at a 10 µg/mL concentration except

for *PA* for which a 22 and 24 μg/mL concentration was needed. For the La(III) complexes the MIC values for all the organisms tested were between 10 and 20 μg/mL.

Taha and collaborators prepared Ln complexes $[LnL(NO_3)_2(H_2O)_x](NO_3)$ {Ln(III) = Nd(III), Dy(III), Sm(III), Pr(III), Gd(III), Tb(III), La(III) and Er(III), x = 0 for Nd(III), Sm(III), 1 for La(III), Gd(III), Pr(III), Nd(III), Dy(III), and 2 for Tb(III)} using as L the tetradentate Schiff base (N,N'-bis(1-naphthaldimine)-o-phenylenediamine) [70]. Their antimicrobial activity against different types of G (+) (*SA*) and G (-) (*SD, PA, EC, PV, Klebsiella, Serratia*) bacteria was assessed by determining their MIC (μg/mL). Though the L showed moderate activity against *PA* and *EC* bacteria, no activity towards the other bacterial strains *PV, SD, SA, Klebsiella* and *Serratia* was registered. Except Er(III) and Dy(III), all the complexes possessed good antibacterial activity against *SA*, La(III) and Pr(III) being the most active ones. Against the G (-) bacteria all complexes showed low activity, however most of them were more active than the free L.

When compared with the standard *Cephalexin* and *Cephradine* (antibacterial agent), it was observed that; (i) several complexes were more potent than the standard antibiotics namely La(III) and Pr(III) complexes against *SA*, Sm(III) complex against *Serratia*, and Gd(III), La(III) and Nd(III) against *PA*; (ii) the rest of the complexes showed no significant activity compared with the standard drugs, and (iii) the G (+) bacteria are much more susceptible than the G (-) bacteria towards the tested Ln(III) complexes probably due to a different composition of the cell wall [70].

In a complementary study of these authors the same complexes were tested against a broader range of G (+) (*SA, Spy, EF*) and G (-) (*EC, KP, PrM, SE, PA*) bacteria [71]. The L had low activity against two (*PrM* and *SE*) of the four G (-) bacterial species used in this study with inhibitory zones within 1–5 mm while the G (+) bacteria (*Spy* and *EF)* were resistant. All the Ln complexes showed good activity in the range 5–15 mm inhibition zones against the G (-) bacterial species except for *KP* which was resistant to all complexes [71].

An year later the authors used N,N'-bis(2-hydroxynaphthylmethyli- dene)-1,3-propanediamine Schiff base L_{III} (Figure 43) to study how different substitutes affect the environment around the Ln center and their biological activity [72].

On one hand, the L_{III} L had moderate activity against *PA* (MIC = 32 μg/mL) and was inactive against *SD* and *PV* whereas all complexes (Figure 44) except Sm–L_{III} exhibited high activity against *PA* with MIC between 2 and 16 μg/mL. Against *SD* only Sm–L_{III} and Dy–L_{III} were active with MICs ranging between 4 and 8 μg/mL, with activity comparable with the ones of the standard antibiotics used. Pr–L_{III} and Dy–L_{III} complexes exhibited higher activity against *PV* than the standard antibiotic used, with MIC of 16 and 4 μg/mL, compared to 125 μg/mL of the antibiotic. On the other hand all G (+) bacteria (*SA, SPy* and *EF*) were resistant to L_{III} and Ln–L_{III} complexes [72].

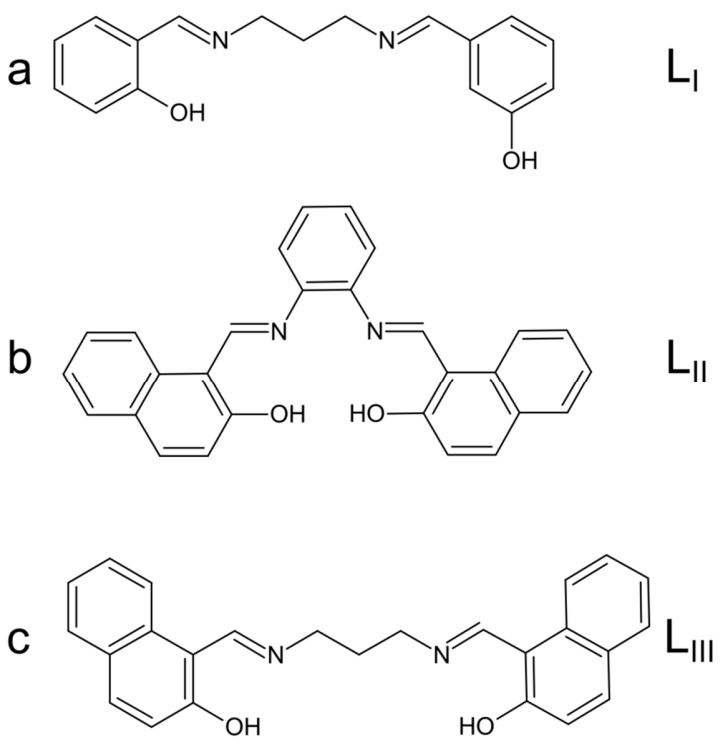


Figure 43. Structures of the Schiff base Ls [72] .

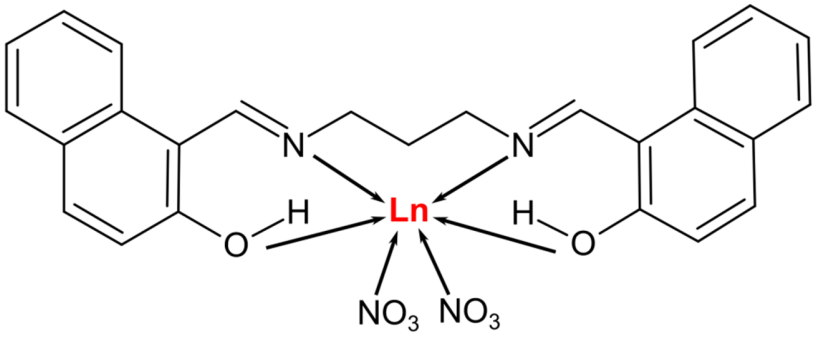


Figure 44. Proposed structure of Ln(III)- L_{III} complexes (Ln(III) = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Tb(III), Dy(III) and Er(III)) [72] .

In most cases the complexes (Ln–L_I, Ln–L_{II} and Ln–L_{III}) exhibited higher antimicrobial activity than the free L (L_I, L_{II}, L_{III}), being Ln–L_I complexes most active against G (-) microorganisms (*PA*, *SD* and *PV*), while the Ln–L_{II} complexes exhibited the lowest activity. The L_I and L_{III} and their complexes were inactive against *EC*, *Serratia* and *Klebsiella*, while all Ln–L_{II}, Sm–L_{II}, and Ln–L_{II} (Ln = Nd(III), La(III), Er(III) and Gd(III)) complexes exhibited moderate to low activity. Ln–L_{II} complexes highly active against *SA* compared to Ln–L_I and Ln–L_{III} complexes [72].

Alghool and collaborators prepared La(III), Ce(IV) and Th(IV) complexes with amino Schiff base [N-(2-hydroxybenzyl)-L-methionine acid](H_3L) [73].

The antimicrobial activity of H_3L (Figure 45) and its Ln complexes (Figure 46) was evaluated against G (+) bacteria (*SA*), G (-) bacteria (*EC*) and two fungi (*AF* and *CA*) and compared with the ones of the standard antibacterial agent *Tetracycline* and standard antifungal agent *Amphotericin B*.

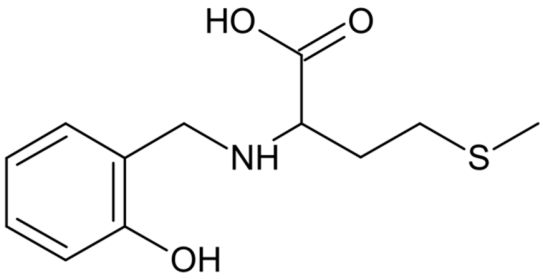


Figure 45. Structure of the 2-(2-hydroxybenzylamino)-4-(methylthio)butanoic acid (H_3L) [73].

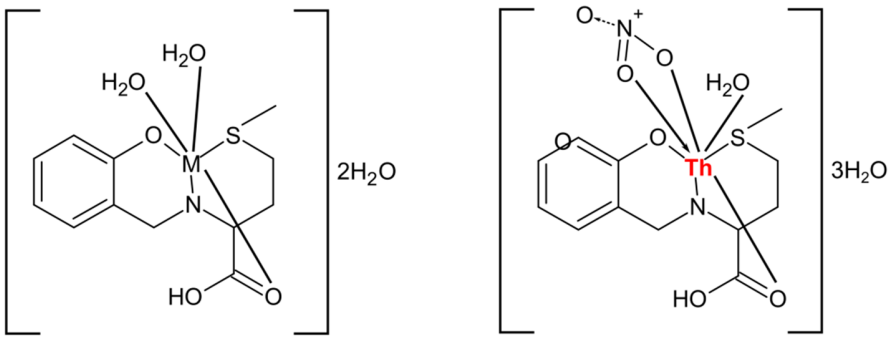


Figure 46. Proposed structure of the metal complexes [73].

Surprisingly, the Ln complexes were less active than the free L and far less active that the standard *Tetracycline* and *Amphotericin B.* All the complexes were inactive against the fungi except La(III) and Th(III) complexes which showed low activity against *CA*. The L showed similar activity against *CA* with La(III) and Th(III) complexes [73].

Ln complexes (Ln = Dy(III), Sm(III), Pr(III), Nd(III), La(III), Er(III) and Gd(III)) with (N, N'-bis (1-naphthaldimine)-o-phenylenediamine), a tetradentate Schiff base were prepared by Al Momani and collaborators [74]. Their antibacterial activity was determined against G (-) (*SD, PV, PA, EC, SM, KP*) and G (+) (*SA*) bacteria. Also, their MICs were determined.

For *SA*, the only G (+) bacteria tested, La(III), Pr(III) and Nd(III) were the most effective, while Er(III) gave the lowest MIC value. G (-) bacteria were less vulnerable to these complexes since higher MIC were needed (32 to 250 µg/mL) for their inhibition. *SD* was susceptible only to Dy(III) with a MIC 250 µg/mL while *PA* which is considered as one of the most recalcitrant bacterial species to various antimicrobials was vulnerable to all complexes. *EC* was also susceptible to all Ln

complexes with relatively higher MIC (63-250 µg/mL). Most of the Ln(III) complexes showed higher activity against both types of bacteria when compared to the free L.

When compared with standard antibiotics *Cephalexin* and *Cephradine* activity, La(III) and Pr(III) complexes were more efficient against *SA*, Sm(III) complex was more active against *SM* and Gd(III), La(III) and Nd(III) were more efficient against *PA* whereas the Ln(III) complexes didn't show significant activity compared with the standard drugs. The authors concluded that the G (+) bacteria were much more susceptible than G (-) towards the Ln(III) complexes due to the complex structure of G (-) compared with G (+) bacteria [74].

Lekha and collaborators reported the synthesis of Ln(III) Schiff base complexes, (Ln(III) = Pr(III), Sm(III), Gd(III), Tb(III), Er(III) and Yb(III)) using sodium salt of Schiff base, 2-[(5-bromo-2-hydroxy-benzylidene)-amino]-3-hydroxypropionic acid (Figure 47) [75]. The complexes with general formula $[Ln(L)(NO_3)_2(H_2O)]\cdot NO_3$ were The Ln complexes were screened against G (-) (*EC, PV, PA*) and G (+) (*SA*) pathogens using agar diffusion method.

The Schiff base L was active due to the presence in its structure of imine group. Though its Ln(III) complexes showed noteworthy antibacterial activity as a result of chelation of metal with organic L, their activity was still lower than the activity of *Ciprofloxacin* used as standard antibiotic [75].

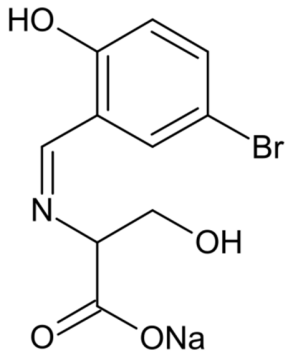


Figure 47. Schiff base L 2-[(5-bromo-2-hydroxy-benzylidene)-amino]-3-hydroxypropionic acid sodium salt [75].

The antibiotic activity of Ln(III) complexes (Ln = La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Yb(III)) with a Schiff base with a general formula $La(HAAP)Cl_3(H_2O)_2]$, was described in the study of Mohanan et al. [76]. The antibacterial activity of L (HAAP) and its Ln complexes (Figure 48) was tested against G (+) (*BM*, *SA*) and G (-) (*EC, ST)* bacteria by the MIC method.

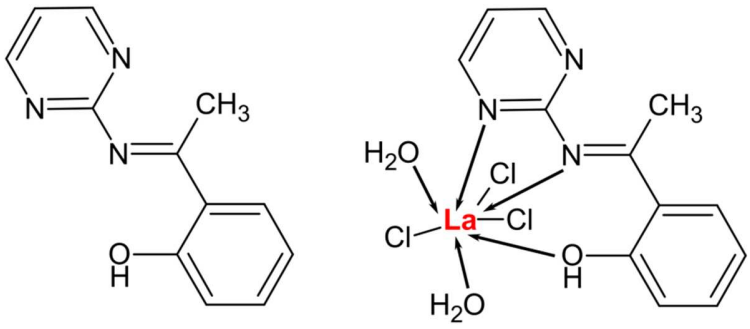


Figure 48. Structure of the L (HAAP) (left) and Structure of [Ln(HAAP)$(H_2O)_2Cl_3$] complexes (right) [76].

All Ln complexes were active with MIC values in the range of 20–60 µg/mL while the MIC value for the L (HAAP) was between 40-66 µg/mL. The most active Ln complex was La(III) complex with MIC values in the range of 20–30 µg/mL. Both the L and the complexes exhibited moderate activity when compared to the standard drug *Ampicillin* with MIC values of 8-12 µg/mL. The results indicated that the complexation with Ln had a synergetic effect on the antimicrobial activity of these compounds and it depended on the type of metal ion [76].

In their attempt to find an efficient antibiotic against methicillin-resistant *SA* (*MRSA*) bacterium (G (+)), Siddappa et al. studied the synthesis of La(III) complex (Figure 49) of (E)-3-((2-hydroxynaphthalen-1-yl)methyleneamino)-2-methylquinazoline-4(3H)-one HNMAMQ Schiff base and tested its antibacterial activity against *MRSA* isolates collected from various hospitals from the Gulbazzrga region.

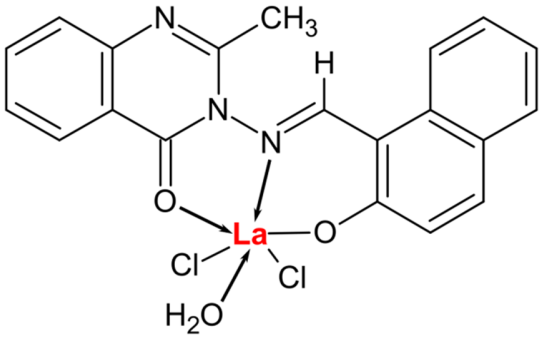


Figure 49. Proposed structure of La(III) complex [77].

The free Schiff base HNMAMQ exhibited good antimicrobial activity against MRSA with a 15 mm inhibition zone, nevertheless, upon complexation with La(III), its antimicrobial activity increase (22 mm). La(III) complex proved to be more active than the free Schiff base with a MIC value of 15 µg/mL whereas the Schiff base MIC was 35 µg/mL. It's worth mentioning that the La(III) complex had the same MIC as the standard *Methicillin* antibiotic representing thus an attractive alternative to the antimicrobial agents used until now to decrease the MRSA incidence [77].

Trivalent Ln complexes of with general formula $[Ln(L)Cl(H_2O)_2]$ (Ln = Nd(III) or Sm(III) and LH_2 = Schiff bases obtained by condensation of 3-(phenyl/substitutedphenyl)-4-amino-5-mercapto-1,2,4-triazole with diacetyl/benzil) (Figure 50) were synthesized and evaluated their antibacterial activity against G (+) bacteria (*BS, SA)* and antifungal activity against *AN, CV* and *CC* in the study of Ain et al. [78].

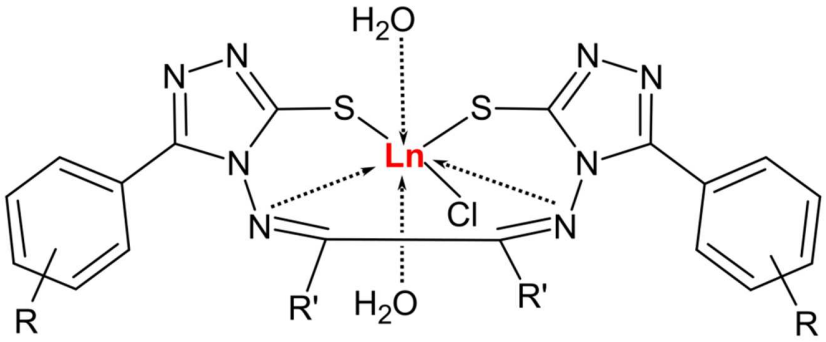
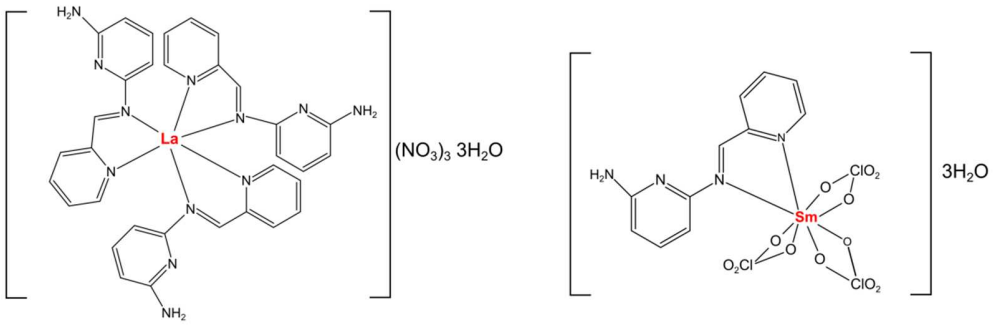


Figure 50. Propose structure for structure of the Nd(III) and Sm(III) complexes [78].

The results indicated that both Schiff bases and their Ln complexes showed antimicrobial activity and moreover, the Ln complexes presented significantly increased antibacterial and antifungal activity in comparison to the free L. The authors proposed that the increased activity of the Ln complexes was due to the presence of N and O donor systems in the L structure which inhibit enzyme activity [78].

Ln complexes (Figure 51) with formula $[La(L)_3](NO_3)_3{\cdot}3H_2O$ and $[Sm(L)(ClO_4)_3]{\cdot}3H_2O$ where L is the Schiff base 2-[(pyridin-2-ylmethylidene)amino]-6-aminopyridine were synthesized by Ali and collaborators [79]. Their antibacterial activity was evaluated against G (+) bacteria (*SA)* and G (-) bacteria (*EC)* using the standard disc diffusion method.



(a) (b)

Figure 51. Proposed structures of (a) La(III) complex and (b) Sm(III) complex [79].

Both Ln complexes showed higher antibacterial activity than the free L due to chelation effect, though their activity was lower that the activity of *Tetracycline* used as standard antibacterial agent [79].

In the study of Ajlouni et al. another Schiff base L [2-thiophenecarboxylic acid, 2-(2-pyridinylmethylene)hydrazide] (Figure 52) and its Ln metal complexes with general formula $[LnL_2(NO_3)_2]NO_3$ (Ln = La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III) and Er(III)]) were synthesized [80].

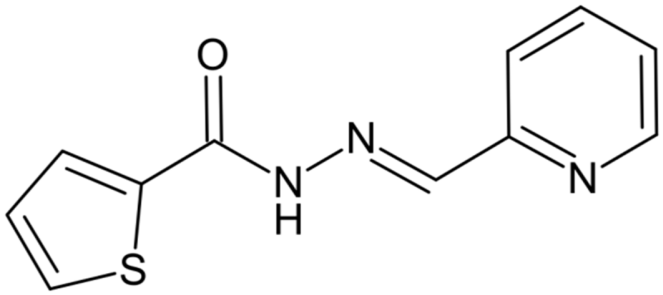


Figure 52. Structure of the Schiff base L [80].

Their antibacterial activity was tested against G (-) (*EC, KP, PrM, SE, PA*) and G (+) (*SA, Spy, EF*) bacteria. The L had an intermediate activity against *PrM* and *SE* and didn't show any activity against the other G (-) and G (+) bacteria. The Ln(III) complexes showed good, moderate, poor and even non-detectible activity against the tested G (-) bacteria. Against G (+) bacteria (*Spy*), Nd(III), Sm(III), Tb(III), Dy(III) and Er(III) were active, whereas against G (-) bacteria these complexes were less efficient, requiring MIC ranging from 16 to 250 µg/mL. *PA* was the most resistant G (-) bacteria to all Ln complexes and free L. *SA* was resistant to both the L and its complexes while against *Spy* and *EF* they exhibited non-detectable to a moderate activity. The increased activity of the complexes compared to the one of the free L can be explained by the chelation effect [80].

Complexes of Ce(III) Schiff base with general formula $[Ce(III)(L)_2(NO_3)_2]NO_3.xH_2O$ [where L = 2-(2,3-dihydro-1H-indolo[2,3-b]phenazin-4(5H)ylidene)hydrazinecarbothio amide (L^1), 3-(ethoxymethylene)- 2,3-dihydro-1H-indolo[2,3-b]phenazin-4(5H)-ylidene)hydrazinecarbothioamide (L^2), (Z)-3-benzylidene-2,3-dihydro-1H-indolo[2,3-b]phenazin-4(5H)ylidene)hydrazine carbothioamide (L^3) were synthesized by Mishra et al. [7]. Their antimicrobial activity was determined against G (+) bacteria (*BS (*ATCC 6633*), SA* (ATCC 6538P)), G (-) bacteria (*EC* (ATCC 25922)) and fungi (*CT* (ATCC 13803) and *AN* (MTCC 282)) using the agar dilution method and compared to activity of standard antibiotic *Amoxicillin*. The results showed that Ln complexes exhibited higher antimicrobial activity than the Schiff base L due to chelation effect which makes the L act as more powerful and potent bacterial agents. On the contrary, the antifungal activity of the Ln complexes was inferior to the activity of the L [7].

Mohanan et al. reported the synthesis of La (III), Ce (III), Pr (III), Nd (III), Sm (III), Eu(III) and Gd(III) chloride complexes (Figure 53) with the Schiff base 2-[N-(20-hydroxy-1-naphthylidene)amino]-3-carboxyethyl-4,5-dimethylthiophene (HNAT) [81]. Their antimicrobial activities against the G (+) (*SA, BS*), G (-) (*EC, PA*) bacterial species and two fungal species (*AN* and *CA*) were examined using disk diffusion method.

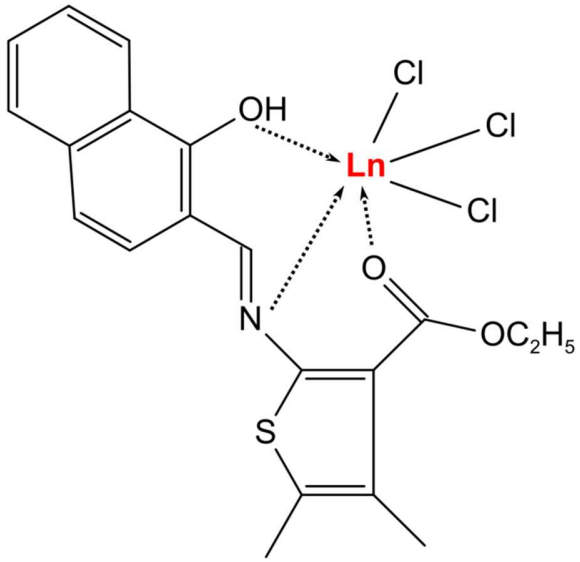


Figure 53. Proposed structure for Ln(III) chloride complexes [81].

Ln(III) chloride complexes exhibited enhanced activity compared to the free HNAT, being La(III) and Nd(III) chloride complexes the most active ones. Though they presented very good antimicrobial activity, their efficiency was still lower than the standard antibiotic *Streptomycin* and standard antifungal *Nystatin*. When comparing the MIC results against the bacterial and fungal strains, the complex with the lowest MIC was La(III) chloride with values of 10 µg/mL against bacteria and 15 µg/mL against fungi [81].

In the study of Shiju et al. Ln complexes of Eu(III), Gd(III), Nd(III), Sm(III), and Tb(III) (Figure 54) with the Schiff base derived from glycylglycine and 4-nitrobenzaldehyde were synthesized and tested for their antimicrobial activity against the bacterial species G (+) (*BS, SA*), G (-) (*EC, PA*) and fungal species (*AN, AF* and *CA*) employing the disc diffusion method [82]. *Amikacin, Ofloxacin* and *Ciprofloxacin* were used as standards for antibacterial activity and *Nystatin* as standard for antifungal activity. The diameters of inhibition zone as well as MIC were determined.

The complexes exhibit moderate to strong antimicrobial activity, being more active against the bacteria rather than the fungi. The most efficient complex was Nd(III) which showed a good activity, especially against the G (-) bacteria such as *EC* and *BS* exhibiting an equal or better activity than the standard antimicrobial agents. Also the Eu(III) and Gd(III) complexes displayed moderate antibacterial activity. Overall, the antimicrobial activity of the complexes is greater than the activity of the free L, indicating that the complexation to Ln increases the activity of the L [82].

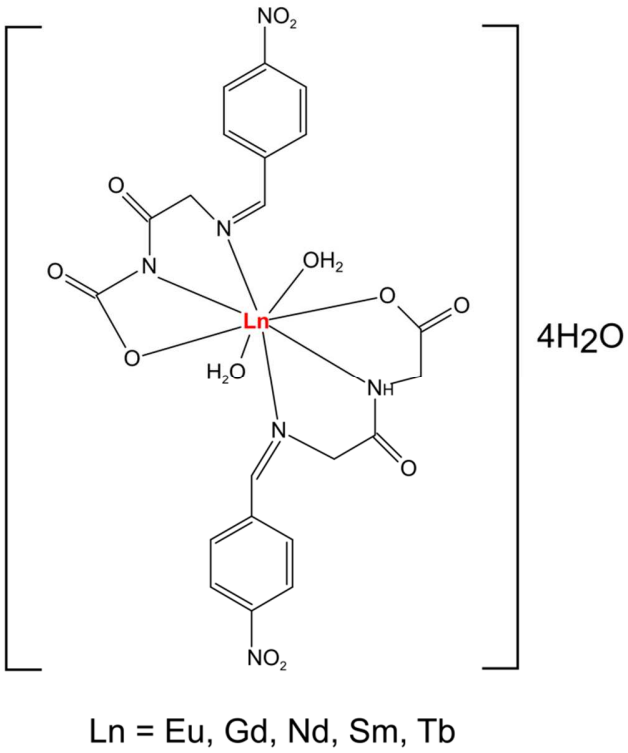


Figure 54. Proposed structure for Ln(III)–4-NBA-GG complexes [82].

Andiappan and collaborators described the synthesis of Er(III), Pr(III) and Yb(III) complexes (Figure 55) with N^2,N^3-bis (anthracen-9-ylmethylene) pyridine-3,4-diamine Schiff base L [83]. Their antibacterial activity was determined against G (+) (*BS, SA*), G (-) (*EC, PA*) bacterial strains in terms of inhibition zone and compared to the standard antibacterial agent *Gentamycin*.

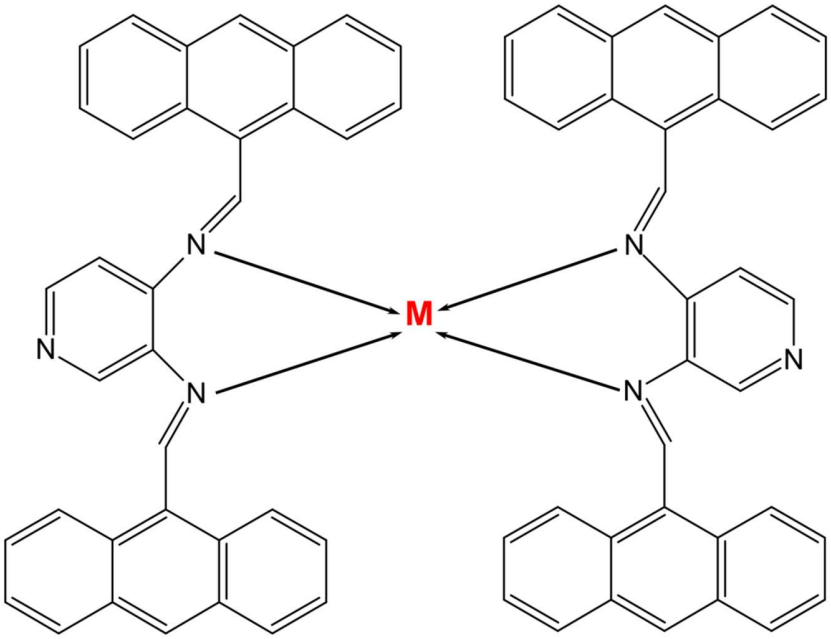


Figure 55. Proposed structure for Schiff base rare earth metal complexes (M = Er(III), Pr(III) and Yb(III)) [83].

The standard *Gentamycin* exhibited antibacterial activity against *BS, SA, EC*, and *PA* with 24, 18, 26, and 25 mm inhibition zone, while among the complexes the maximum inhibition zone (19 mm) against *EC* was obtained with Er(III) complex. On the other hand, with Pr(III) complex superior antibacterial properties were obtained against *BS, SA, EC* and *PA*, with maximum inhibition zone of 20, 17, 20, and 23 mm, comparable to *Gentamycin* activity. Similar results were obtained with Yb(III) complex against all pathogens. Pr(III) complex showed better antibacterial properties than the Er(III) and Yb(III) complexes with low MIC values against all the pathogens.

Conclusions

New emerging and re-emerging infectious diseases caused by G (+) and G (-) bacteria, represent a real threat due to their epidemic potential. In this context, the discovery and development of new antimicrobial drugs are urgently required. The biological activity of Ln has been studied for several decades and it was proven that they possess antimicrobial activity. In this review we gathered all the studies published since 1995 dealing with Ln(III) complexes application as antimicrobial agents. It was reported that upon complexation with Ln ions, the activity of the parent L is enhanced due to the increase lipophilicity which allows Ln complexes to penetrate through the lipid membranes of the cell and cause the disturbance of the normal functioning of the cell which will finally lead to cell death. Generally, the antibacterial activity of the Ln complexes was stronger than the antifungal activity due to the different composition of the cell wall which makes fungal wall more difficult to penetrate. In some cases Ln complexes exhibit antimicrobial activity similar or even better than the activity of standard antimicrobial agents thus representing a possible alternative to antimicrobial agents used currently. Thought more studies

are needed, Ln complexes may represent a possible alternative to antimicrobial agents used currently.

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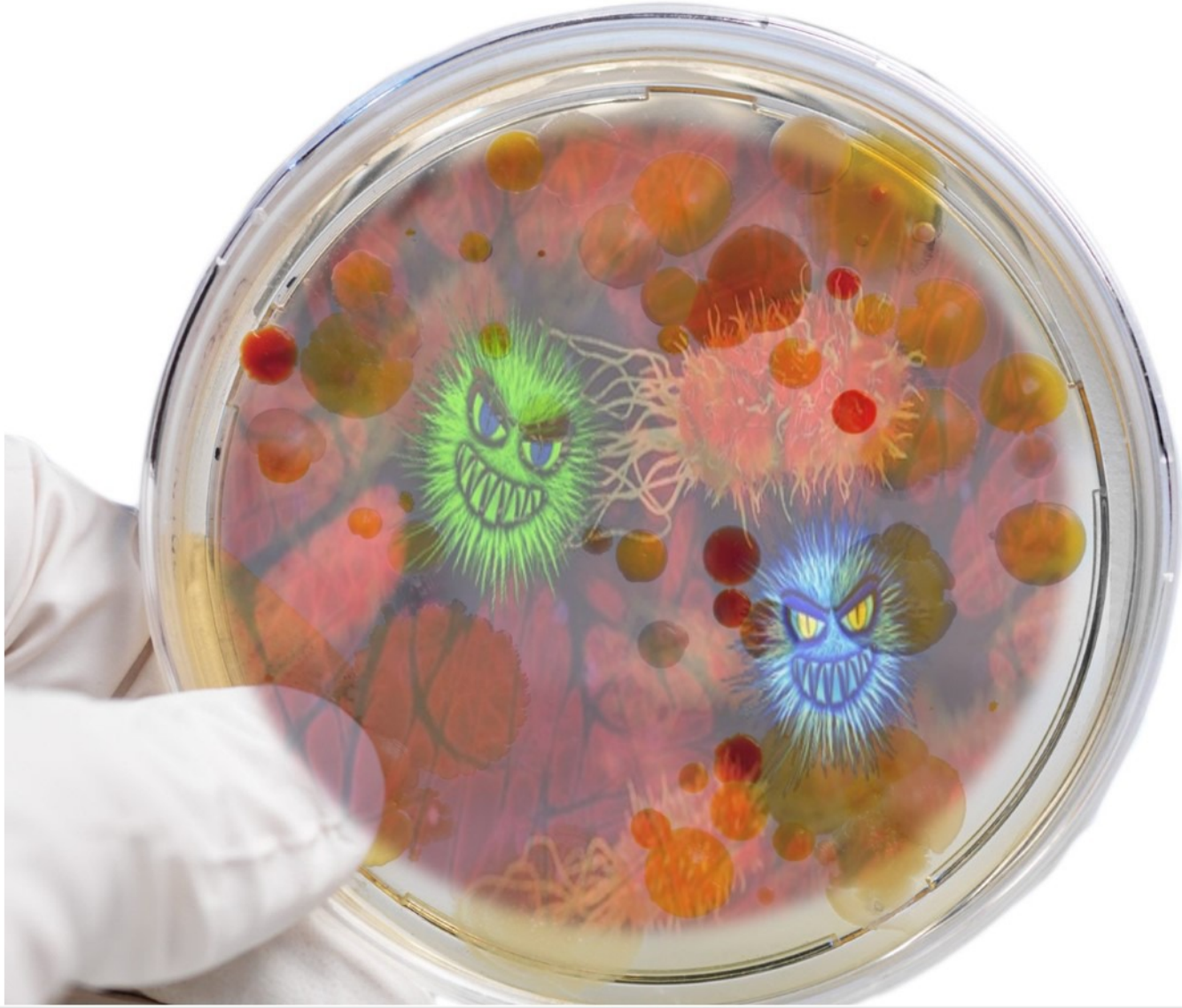

Lanthanides														
Lanthanum	Cerium	Praseodymium	Neodymium	Promethium	Samarium	Europium	Gadolinium	Terbium	Dysprosium	Holmium	Erbium	Thulium	Ytterbium	Lutetium
57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu