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REVIEW

Anti-bacterial Properties of Transition Metal Complexes of Copper Metal Ion: A Mini Review

Abhay Nanda Srivastva[1,2*] Nisha Saxena[3] Netra Pal Singh[4] Jayant Kumar[5]

1. Department of Chemistry, Nitishwar Mahavidyalaya, B. R. A. Bihar University, Muzarrafpur, 842002, India
2. University Department of Chemistry, B. R. A. Bihar University, Muzaffarpur, 842001, India
3. Department of Chemistry, M. R. M. College, L. N. Mithila University, Darbhanga, 846004, India
4. Department of Chemistry, D. D. U. Gorakhpur University, Gorakhpur, 273009, India
5. Graduate Student, Department of Zoology, Nitishwar Mahavidyalaya, B. R. A. Bihar University, Muzarrafpur, 842002, India

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ABSTRACT

Bacterial infections are a major cause for impulsive deaths in human beings. Bacterial infections of the respiratory, gastrointestinal and central nervous system account for the majority of cases of sudden casualties. Readily available drugs are getting ineffective by each passing day as the mutation is very fast in these pathogenic microbes resulting in drug resistance. The growing resistance of bacteria necessitates the development of new and effective compounds of desired characteristics that could bar the rapid development of bacterial cell inside of the host body. Along with cellular resistance for clinical antibiotics, co-bacterial infections during microbial attacks (*viz.* virus, fungus, protozoans etc.) also demand for some novel antibacterial drugs having high efficacy and minimal side effects on human body. These antibiotics should also be compatible with remedies ongoing for core microbial infections. So, in demand of search for effective antibacterial moieties, the scope of transition metal complexes as drug gives a good signal against the pathogenic bacteria by inhibiting their growth. The action of metal complexes on bacterial cell may be due to impremiablity, enzymatic interruptions, ribosomal interactions, disturbance in the path of protein synthesis, denaturing of genetic materials etc. inside the cell. Metals in complexes may interrupt the lipophilisity through the bacterial cell wall. Inclusion of metal ions in organic moieties behaving as ligand delocalize π-electrons upon the entire chelate ring and this chelation results in overlapping of ligand orbital and partial sharing of (+)ve charge of metal ion with donor atoms. These structural modifications in metal and organic lone pair donor species are the supposed reasons for their enhanced antimicrobial activities against pathogenic microbes. The present review focuses on the impact of recently synthesized, well characterized mono and binuclear transition metal complexes of Cu ions that have the potential to be the drug of the decade in medicinal inorganic chemistry for treating the bacterial diseases.

*Corresponding Author:
Abhay Nanda Srivastva,
Department of Chemistry, Nitishwar Mahavidyalaya, B. R. A. Bihar University, Muzarrafpur, 842002, India; University Department of Chemistry, B. R. A. Bihar University, Muzaffarpur, 842001, India;
Email: abhay_s1986@yahoo.co.in

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1. Introduction

Discovery of *cis*-platin opened the door for the exploration of an enormous number of other biologically active metal complexes [1,2]. It was then a new interest of the pioneer to synthesize novel transition metal complexes. Transition metals complexes with metal ion/s and a variety of ligands developed from organic and/ or inorganic moieties were of interest of chemists for the structural elucidation and their applications in various emerging field of science and technology [3,4]. Transition metal complexes have shown their importance in all the area of chemistry serving to society [5-7]. Among different applications, metal complexes are studied as potent drug molecules against many day to day life diseases to lethal diseases, *viz.* general microbial infections, diabetes, inflammation, cancer, acquired immune deficiency syndrome, Alzheimer, Parkinson etc. Among various therapeutic potentials, antimicrobial applications of metal complexes are the centre of attention for medicinal chemists due to resistance of pathogenic microbes against traditional antibiotics developed from organic synthons [8-10]. Copper was known well for its anti-microbial as well as therapeutic properties from a very long time [11]. Now, its ionic complexes are studied as drugs in modern medical sciences and are of interest among medicinal chemists for evaluating drug likeness behaviour against various lethal diseases [12-16]. In recent years, copper metal ions became very popular along with other transition metal ions for the study of antibacterial properties along with antifungal and anticancer properties of transition metal complexes on both Gram positive and Gram negative bacteria and other microbes and cancer lining cells, respectively [14,17-37]. In the current pandemic of COVID-19, many metal complexes including copper have been tested and found effective against various strains of corona virus by *in silico* mean [12,13]. Transition metal complexes of copper metal ions on a variety of ligands have shown promising results on pathogenic Gram positive bacteria such as *S. aureus, B. subtilis*, *E. Faecalis, S. mutans*, *S. gordonii*, *B. cereus* and Gram-negative bacteria such as *E. coli* and *S. typhi*, *P. aeruginosa* and *K. pneumonia*, *V. cholera* and *S. pneumonia* [17-20]. The final activities of different transition metal complexes of copper ions are different on tested organisms as it largely depends on either the impermeability of cells of organisms or the difference in the ribosome of bacterial cells as well as on the nature of ligands used to prepare the complexes [38-43]. In the present review, we tried to set a view of antibacterial efficacy of copper based metal complexes in front of global researchers to drag their attention for further discoveries and researches to find copper metal complexes as potent antibacterial medicinal agent.

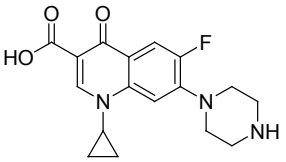
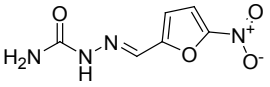
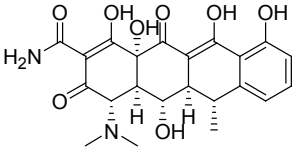
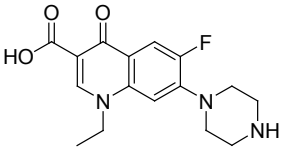
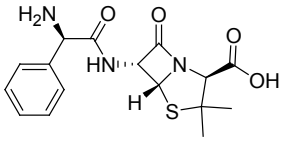
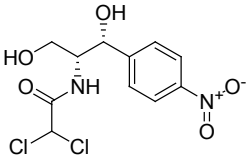
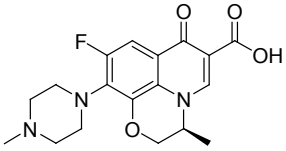
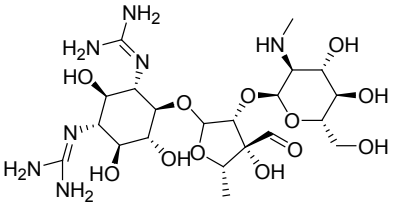
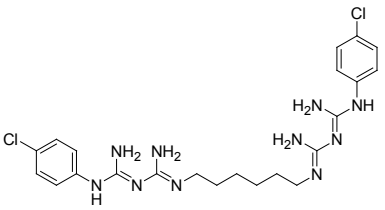
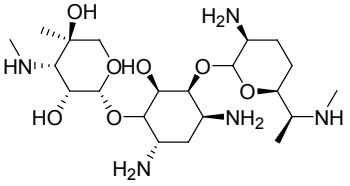
2. Historical Developments for Antibacterials

The treatment of bacterial infections approved by administration of chemotherapeutic agents, the therapy was began in the 1930s, and was one of the most profound medical advances occurred in twentieth century. All the antibacterial drugs in clinics today were developed by drug discovery programmes and systematic studies leads to identify inhibitors by tracing their mode of action and ability to prevent bacterial growth. The 'golden period' of antibacterial-drug discovery was laid between the 1940s and 1970s [44,45]. The development of these therapeutics or agents derived from them helped a lot to combat the disease burden. In the meanwhile the emergence of resistance to antibiotics in pathogenic bacteria worldwide during the past three decades threatened the public health globally and challenged the medicinal chemist profoundly. This could destabilize the major advances achieved in the treatment of infection so far [46-49]. The developments in molecular modelling, bioinformatics, biochemistry and target-based drug discovery program advances the current strategy for finding and develop therapeutics as antibacterial. Though molecular targets for effective antibacterials are fairly few but they are found to involve consistently in the pathways of macromolecular synthesis. They are indeed, the essential components and comprise for functioning of bacteria that cannot be satisfied by providing intermediates. Especially, very few targets of the major classes of antibacterials used in systemic mono-therapy are essential enzymes present in bacterial cell. Some clinical antibacterial drugs used as reference in antibacterial evaluation of metal complexes are listed in Table 1 along with their IUPAC name and chemical structure.

3. Antibacterial Activity of Mononuclear Copper Complexes

Some of the considerable mononuclear copper metal complexes on different ligands were synthesized and screened for their anti-microbial and anti-tumour activities. Transition metal complexes of copper such as $[Cu(L_1)_2]\cdot 2H_2O$, $[Cu(L_2)_2]\cdot 2H_2O$, $[Cu(L_3)_2]\cdot 2H_2O$, $[Cu(L_4)_2]\cdot 2H_2O$ have been prepared by deprotonation of Schiff base ligands (HL_1–HL_4) designed by condensation of 4-Fluorobenzylamine with 2-Hydroxy-1-naphthaldehyde/3,5-Dichlorosalicylaldehyde/3,5-dibromosalicylaldehyde/3-Bromo-5-chlorosalicylaldehyde. All of these metal complexes were characterised using different physiochemical techniques and the spectro analytical data favours well the proposed structure of synthesized ligands and metal complexes [19]. Also *in vitro* screening of these well screened ligands and metal complexes of Cu

Table 1. Chemical structure and IUPAC name of some antibacterial drugs taken as standard/ control during in vitro antibacterial activity screening of ligands and metal complexes.

S.N.	Drug	Chemical structure	IUPAC Name	Ref.
1	Ciprofloxacin		1-Cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid	[50]
2	Furacilinum / Furacine		[(E)-(5-nitrofuran-2-yl)methylideneamino]urea	[50]
3	Doxycycline		(4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide	[50]
4	Norfloxacin		1-ethyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid	[50]
5	Ampicillin		(2S,5R,6R)-6-[[(2R)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	[51]
6	Chloramphenicol		2,2-dichloro-N-[(1R,2R)-1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]acetamide	[51]
7	Levofloxacin		(2S)-7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo[7.3.1.05,13]trideca-5(13),6,8,11-tetraene-11-carboxylic acid	[50]
8	Streptomycin		2-[(1R,2R,3S,4R,5R,6S)-3-(diaminomethylideneamino)-4-[(2R,3R,4R,5S)-3-[(2S,3S,4S,5R,6S)-4,5-dihydroxy-6-(hydroxymethyl)-3-(methylamino)oxan-2-yl]oxy-4-formyl-4-hydroxy-5-methyloxolan-2-yl]oxy-2,5,6-trihydroxycyclohexyl]guanidine	[51]
9	Chlorhexidine		(1E)-2-[6-[[amino-[(E)-[amino-(4-chloroanilino)methylidene] amino]methylidene]amino]hexyl]-1-[amino-(4-chloroanilino) methylidene]guanidine	[50]
10	Gentamycin		(2R,3R,4S,5R)-2-[(1S,2R,3S,4S,6S)-4,6-diamino-3-[(2S,3S,6S)-3-amino-6-[(1S)-1-(methylamino)ethyl]oxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino) oxane-3,5-diol	[51]

yielded some fruitful results when tested against Gram positive *S. gordonii and S. aureus* and Gram negative *E. coli* and *P. aeruginosa* with Ciprofloxacin as a standard reference. $[Cu(L_3)_2]\cdot 2H_2O$ showed the most promising results against Gram positive while $[Cu(L_4)_2]\cdot 2H_2O$ showed the most promising result against Gram-negative under laboratory conditions among other metal complexes used in this screening process [19]. Copper complexes of formulae $[Cu(L)_2]\cdot H_2O$, $[Cu(Br)(L)]\cdot H_2O\cdot CH_3OH$, $[Cu(L)Cl]\cdot C_2H_5OH$ of ligand 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone-4-ethylthiosemicarbazone were prepared, purified and screened against Gram positive bacteria *B. cereus* and *S. aureus* and Gram negative *S. abony* using Furacilinum as the standard reference [20]. In results, the metal complexes appeared to be impactful against screened bacteria [20]. Transition metal complex $[Cu(L)_2]$ of crystal X-ray studied ligand 1-(2-nitrobenzylidene)-2-(phthalazin-1-yl)hydrazine was synthesized and characterized by spectral and physical methods viz. IR, UV-vis., NMR, Mass, TGA etc. and then tested for its antibacterial activity against Gram positive *E. faecalis*, *S. mutans* and *S. aureus* and Gram negative *E. coli, P. aeruginosa* and *K. pneumoniae* taking Ciprofloxacin as the standard reference drug and the inhibition capacity of the metal complex, in this case, is accordingly to the inhibition of the ciprofloxacin [18]. Organic ligandsamidino-O-methylurea (L^1), N-(benzyl)-amidino-O-methylurea (L^2), 2,2′-bipyridine (bipy) and 1,10-phenanthroline (phen) were applied to produce a series of mixed ligand copper complexes with formulae $[Cu(L^1)(bipy)].Cl_2$, $[Cu(L^1)(phen)].Cl_2$, $[Cu(L^2)(bipy)Cl_2]$ and $[Cu(L^2)(phen)].Cl_2$ possessing antibacterial properties. Antibacterial potency order of tested complexes were predicted as $[Cu(L^1)(phen)].Cl_2 > [Cu(L^2)(phen)].Cl_2 > [Cu(L^1)(bipy)].Cl_2 > [Cu(L^2)(bipy)Cl_2]$ against three Gram negative bacterial strains E. coli, Salmonella and Campylobacter. The best inhibition action was performed by $[Cu(L^1)(phen)].Cl_2$ against *Campylobactor* [52]. Well characterized copper (I) halide complexes $[Cu(L^1)_2Cl]$, $[Cu(L^1)_2Br]$, $[Cu(L^1)_2I]$, $[Cu(L^2)_2Cl]$, $[Cu(L^2)_2Br]$, $[Cu(L^3)_2Br]$ coordinated with S atoms of thiocarbamide fragments of 4-thioxo[1,3,5] oxadiazocines ligands (L^1- L^3) were evaluated for their antibacterial potential via bioluminescent toxicological assay against E. Coli K12 TG1 bacterial strain and results were compared with free ligands and standard antibacterial drugs Doxycycline, Norfloxacin, Ciprofloxacin, Ampicillin and Chloramphenicol. The complexes of L^1 and L^2 ligands occupied with electron dragging groups showed stronger activity comparable activity to reference drugs against targeted microbial strain [53]. Bioactive Cu(II) mixed ligand complexes [Cu(Lvx)(Dpya)Cl]·Cl and [Cu(Lvx)(Dphen)Cl]·Cl of commercial antibiotic levofloxacin (Lvx) with 2,2′-dipyridylamine (Dpya) and 4,7-Diphenyl-1,10-phenanthroline (DPhen), respectively [Figure 1: i, ii, iii (ligands); Figure 2: 1, 2 (complexes)] were reported active against four Gram positive *S. aureus*, *B. subtilis*, *E. faecalis* and *S. pneumoniae* and five Gram negative *P. mirabilis*, *S. flexneri*, *E. coli*, *Citrobacter* species and *S. typhi* bacterial cells. Antibacterial activity was evaluated *in vitro* by disc diffusion method in agar media as nutrient and results were compared with levofloxacin as parent ligand and neomycin as reference drug. Antimicrobial activity data obtained clearly indicate that inhibition potential of both copper complexes is much higher than the free levofloxacin and metal salt tested against targeted bacterial strains [54]. Methicillin resistant bacteria *S. aureus* and *P. aeruginosa*, *E. coli, M. vaccae, B. subtilis* pathogenic bacterial strains were targeted to evaluate antibacterial efficacy of four novel copper complexes with chiral properties synthesized from terpene derived ethane-1,2-diamine ligand [Figure 1: iv, v, vi, vii (ligands); Figure 2: 3, 4, 5, 6 (complexes)]. Structural elucidation of prepared compounds was done with the help of advance physico spectral techniques and well supported as proposed. IR and NMR data revealed bidentate behaviour of ligands iv-vi, while the ligand viii acts as tridentate in coordination with copper metal ions. The *in vitro* antibacterial potential of all copper complexes was reported comparable to the standard medicine ciprofloxacin used as reference drug [55]. Gram positive *S. aureus*, *B. subtilis* and Gram negative *E. coli*, *S. typhimurium* bacterial strains were targeted by mononuclear complexes (7-14) of acetate, chloride, nitrate, sulphate salts of copper metal ion with a novel hydrazone ligand and/or 8-hydroxyquinoline , 1,10-phenanthroline, benzoylacetone as mixed ligands [Figure 1: viii(H_2L^1), ix(HQ), x(Bac), xi(Phen) ligands; Figure 2: 7, 8, 9, 10, 11, 14 (complexes)]. Antibacterial activity data, in vitro, indicate that the ligand and their metal complexes; $[(HL^1)Cu(OAc)(H_2O)]\cdot 1.5H_2O$ (7), $[(H_2L^1)Cu(SO_4)(H_2O)_2]\cdot 1.5H_2O$ (8), $[(HL^1)Cu(H_2O)_3]\cdot Br\cdot H_2O$ (9), $[(HL^1)Cu(HQ)(H_2O)]$ (10), $[(HL^1)Cu(H_2O)(Bac)]\cdot 2H_2O$ (11) showed a buoyant activity against the Gram positive bacteria; *B. Subtilis*, but complexes $[(HL^1)Cu(H_2O)].NO_3$ (12), $[(HL^1)CuCl]\cdot 1.5H_2O$ (13), $[(HL^1)Cu(OAc)(Phen)]$ (14) showed no effect even. Targeted strains of *S. aureus*, *E. coli*, and *S. typhimurium* were unaffected by test compounds H_2L^1 and all copper complexes [56]. 2-cetylpyridinenicotinichydrazone; HL as ligand applied to synthesize copper complexes as $[Cu(L)_2]$, $[Cu(HL)Cl_2]$ and $[Cu(HL)Br_2]$ in 1:2, 1:1 and 1:1 metal ligand ratio (M : L), respectively. These complexes were well characterized by single X-ray crystallography along with IR, UV-vis., NMR and

Mass spectral techniques. Spectral studies supported well the proposed structure, coordination mode and geometry of copper complexes. These complexes and ligand were studied for the evaluation of in vitro antibacterial potential against *S. mutans, S. mitis, S. sanguinis, S. sobrinus, L. casei, S. salivarius* and *E. faecalis* bacterial strains. Minimum inhibitory concentration of dilutions of ligands and complexes were observed and compared with Chlorhexidine as standard antibacterial drug. The minimum inhibitory concentration data showed the enhanced activity of complexes than free ligand and satisfactory as compared to standard control drug [57].

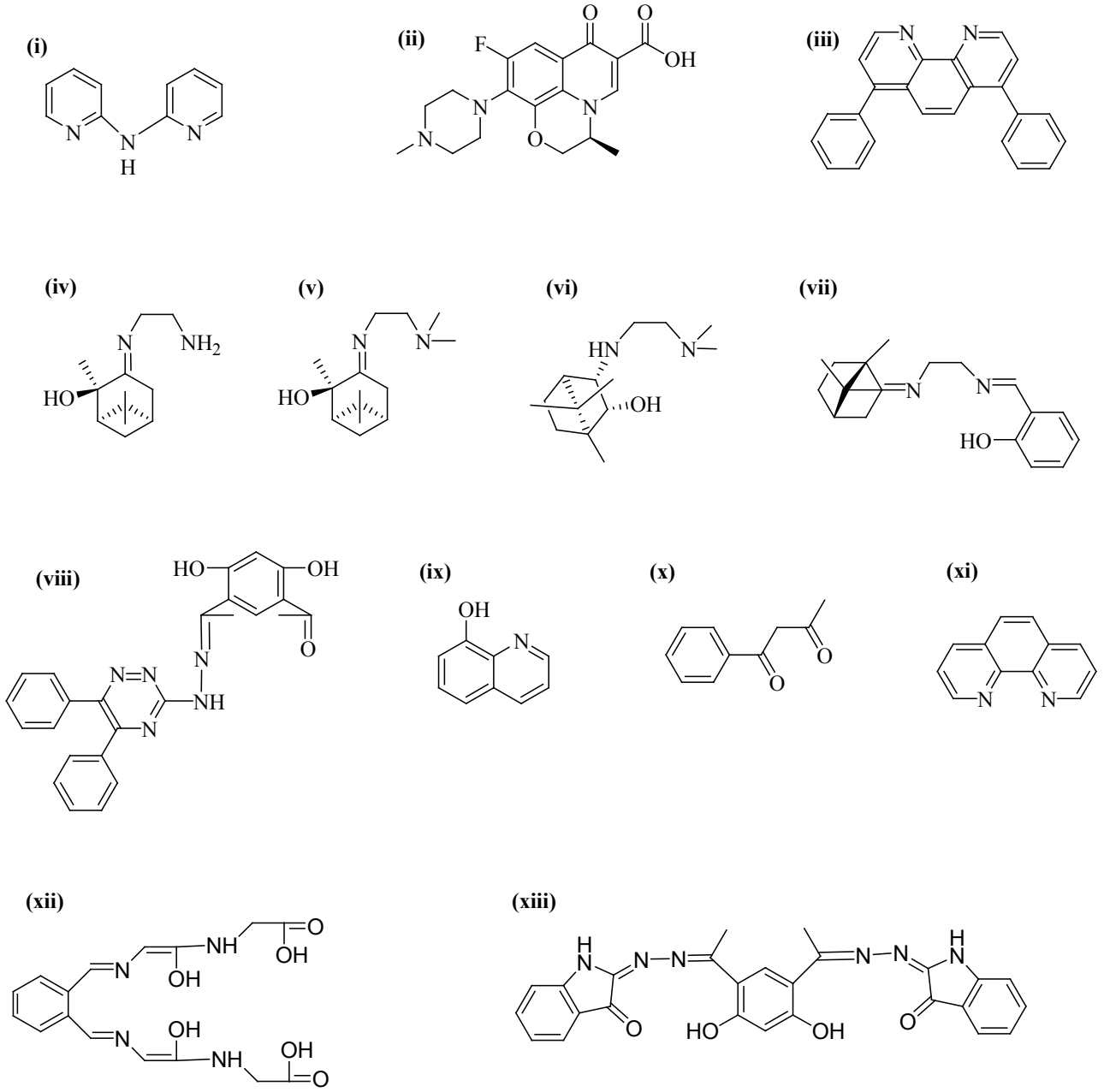


Figure 1. Structure of some antibacterial ligands (i-xiii) applied to prepare copper complexes [53-56]

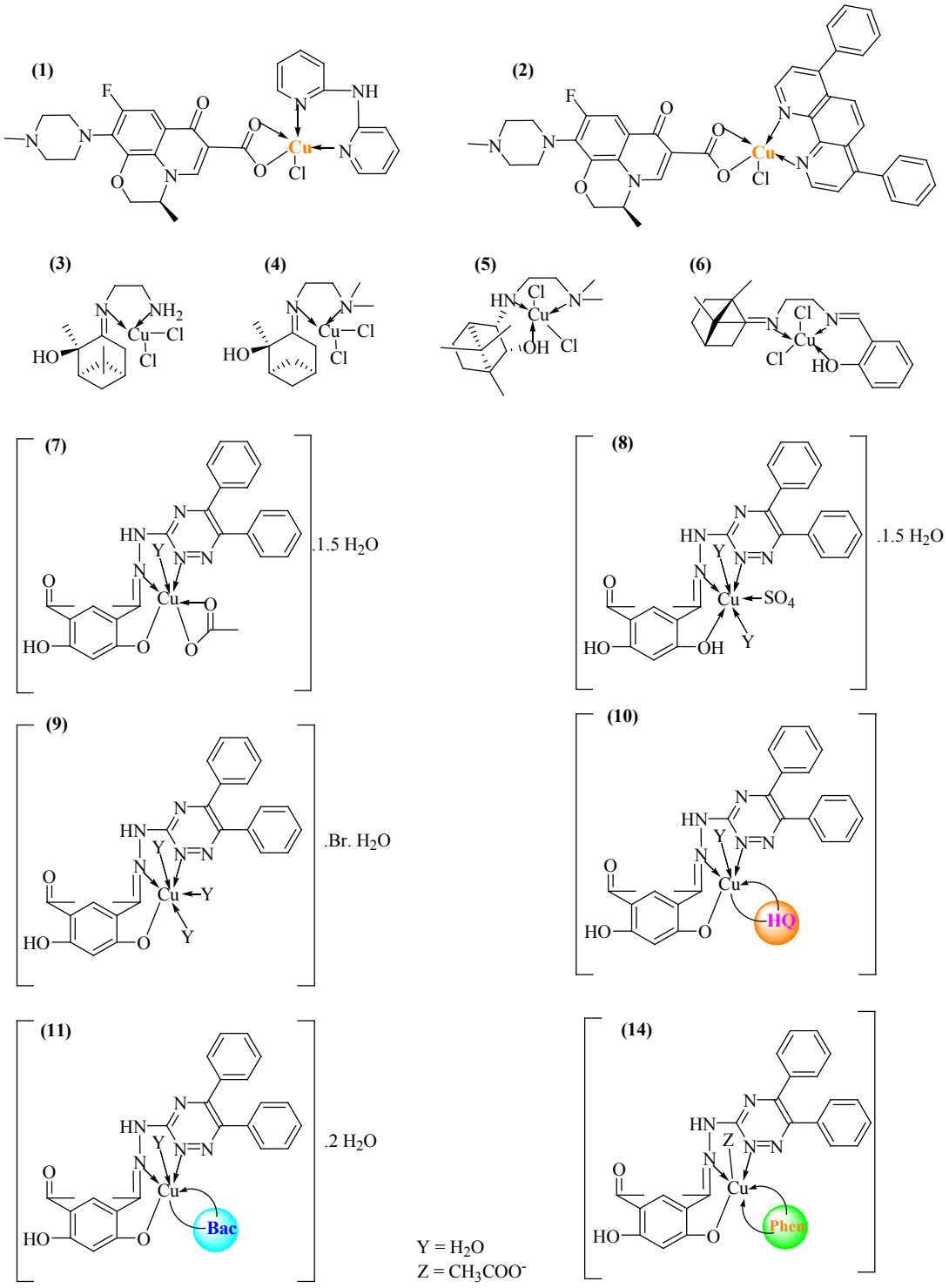


Figure 2. Structure of antibacterial copper complexes (1-11, 14) of ligands (i-vii) [53-56]

4. Antibacterial Activity of Bi-nuclear Copper Complexes

Along with the synthesis of mononuclear metal complexes, a big number of binuclear metal complexes were also synthesized and have been tested for their anti-microbial activities. Transition metal complexes of a copper metal ion such as $[Cu_2(Pym\ L)Cl_3]$ on the Schiff base and Pyrimidine-derivative ligands was synthesized by template condensation of Schiff base (L) derived from glycine using 2,3-butanedione, 5-methyl-2,6-pyrimidine-dione and metal chloride/acetate salt in 1:1:2

stoichiometric ratio [17]. Synthesized compounds were well characterized by its elemental analysis, magnetic measurement and other physiochemical techniques. Tetra dentate coordination behaviour of Schiff base (L) and tridentate behaviour of 5-methyl-2,6-pyrimidine-dione (Pym) was executed by IR and NMR spectral studies. Octahedral environment surroundings of copper metal ions are revealed by UV-visible and EPR spectral studies. These structurally elucidated compounds were then screened for their antibacterial activities by taking Streptomycin as a standard reference against Gram-positive *S. aureus* and *B. subtilis* and Gram-negative *E. coli* and *S. typhi*. The Cu compound showed some excellent result against Gram-positive bacteria and a good result against Gram negative bacteria under laboratory conditions [17]. $[Cu(NO_3)(L)]_2 \cdot C_2H_5OH$ of ligand 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone-4-ethyl-thiosemicarba-zone were prepared, purified and screened against Gram positive bacteria *B. cereus* and *S. aureus* and Gram negative *S. abony* using Furacilinum as the standard reference [21]. In results, the metal complexes appeared to be impactful and showed some excellent results against screened bacteria [21]. Bioactive $[Cu_2(L)(H_2O)_4]$ have been synthesized with a Schiff base ligand derived from diglycine and benzene-1,2-dicarbaldehyde [Figure 1: xii (ligand); Figure 3: 15 (complex)] and evaluated for its *in vitro* antibacterial

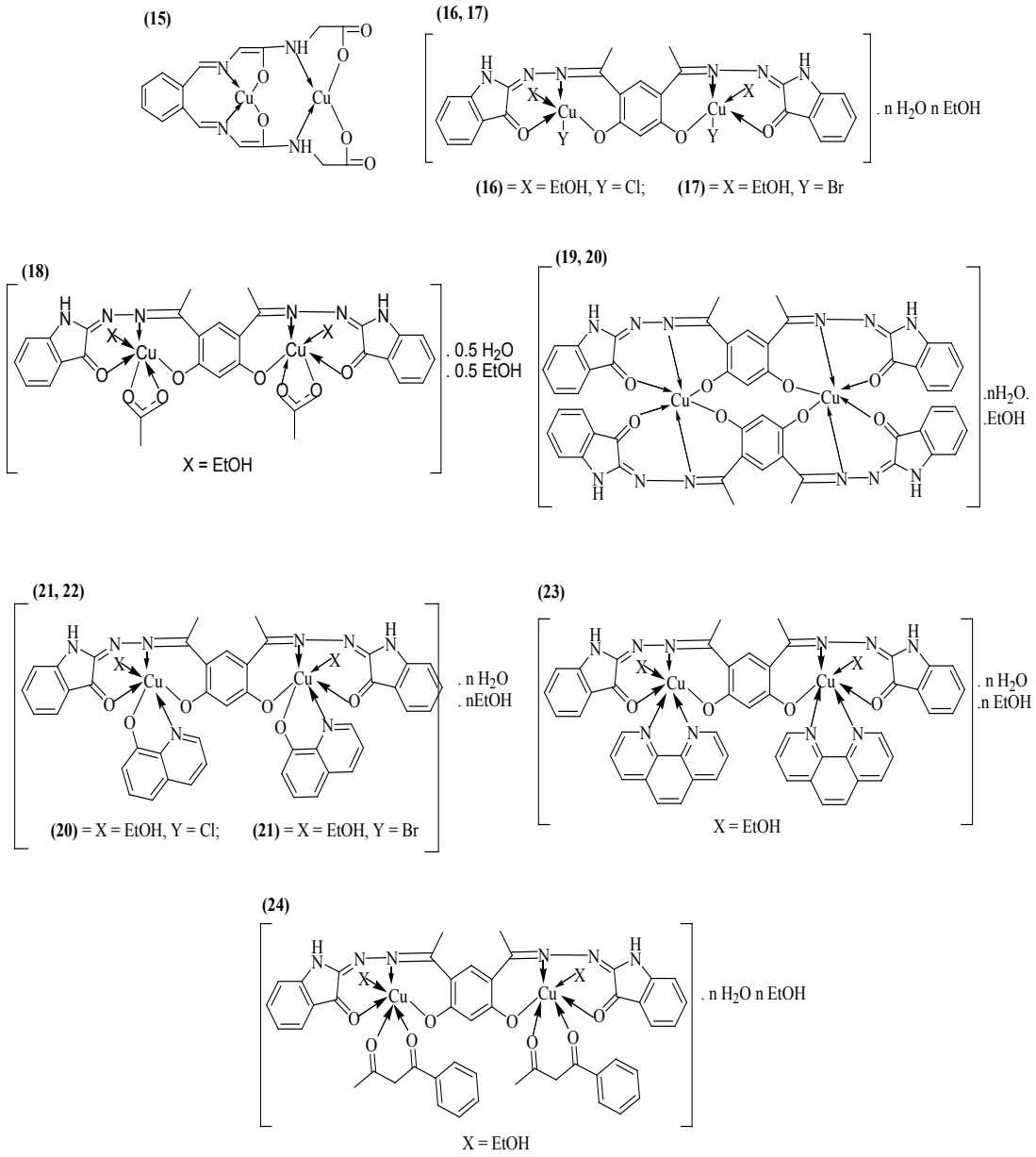


Figure 3. Structure of antibacterial bimetallic copper complexes (15-24) with ligands (xii-xiii) [56-60]

activity at the concentration of 10^3 g/Ml against *B. subtilis and S. aureus, E. coli and K. pneumonia* bacterial strains in the presence of three reference drugs streptomycin, ampicillin and rifampicin. The zone inhibition potential of copper complex was found much improved than free ligand [58]. Deprotonation of a potent ligand, *N*,*N*′-*bis*(*N*-hydroxyethylaminopropyl)oxamido (H_2heap) resulted in the formation of a hydrated binuclear copper complex $[Cu_2(heap)]\cdot(ClO_4)_2\cdot 2H_2O$ on reaction with perchlorate salt of copper metal ion. Bioactivity of complex was evaluated against bacterial strains of *S. aureus, E. coli, B. subtilis* and recorded enhanced antibacterial potential than free ligand *in vitro* [59]. Copper complex of methoxy thiosemicarbazone (MTSC) of formulae $[Cu(MTSC)(NH_3)_3(-Cl)]\cdot 2H_2O$ (12) and $[Cu_2(MTSC)(NH_3)_4(Cl)_2(H_2O)_2]\cdot 2H_2O$ (13) were prepared and tested for their antibacterial potential against *B. subtilis, S. aureus, E. coli and P. vulgaris* with Gentamycin as reference drug. The inhibition potential data indicate that metal complexes have greater potential than free ligand [60]. 4,6-diacetylresorcinol and isatin monohydrazone yielded ligand (H_2L^2) and then allowed to react with Cu^{+2} ion salts in 1:1 and 2:1 stoichiometric ratio resulting bioactive binuclear copper complexes [Figure 1: xii, xiii (ligands); Figure 3: 16-20 (complexes)]. H_2L^2 was further reacted with Cu^{+2} metal ions along with 8-hydroxyquinoline, 1,10-phenanthroline, benzoylacetone to produce mixed ligand binuclear complexes [Figure 1: ix-xi, xiii (ligands); Figure 3: 21-24 (complexes)]. *In vitro* antibacterial activity data assessment divulged that the ligands (H_2L^2) showed activity against *S. aureus*, *B. subtilis* and *E. coli* bacteria. Complexes showed good activity against studied bacteria comparative to free ligand [56].

5. Conclusions

Precisely the transitional metal complexes of copper metal ion can possess antibacterial properties as seen in the different research activities performed by a different group of people around different times. Also, it gives us hope towards achieving new heights in the field of antibacterial drugs. As we have seen during the pandemic of COVID-19, bacterial/fungal co-infections have also raised along with deadly corona virus infections and these co-infections thus increased the mortality rate in corona virus infected patients throughout the globe. The impact of readily available antibiotic drugs getting reduced by many folds because the increasing drug resistance capabilities of the bacteria, these metal complexes based drugs can help us in controlling the damage due to these deadly bacterial infections. These complexes are the hope of future medicinal chemistry as the organic-based drugs are getting ineffective against growing drug resistance of these bacteria. The depth studies of copper coordinated metal complexes based on structural and antibacterial potential along with their synthetic route and mode of action may fulfil the future need of effective antibacterial drug for specified target microbe.

Abbreviations

Acronym	Full word
S. aureus	*Staphylococcus aureus*
B. subtilis	*Bacillus subtilis*
E. Faecalis	*Enterococcus faecalis*
S. mutans	*Streptococcus mutans*
S. gordonii	*Streptococcus gordonii*
B. cereus	*Bacillus cereus*
E. coli	*Escherichia coli*
S. typhi	*Salmonella typhi*
P. aeruginosa	*Pseudomonas aeruginosa*
K. pneumonia	*Klebsiella pneumonia*
V. cholera	*Vibrio cholera*
S. pneumonia	*Streptococcus pneumonia*
S. abony	*Salmonella abony*
P. mirabilis	*Proteus mirabilis*
S. flexneri	*Shigella flexner*
M. Vaccae	*Mycobacterium vaccae*
S. typhimurium	*Salmonella typhimurium*
S. mitis	*Streptococcus mitis*
S. sanguinis	*Streptococcus sanguinis*
S. sobrinus	*Streptococcus sobrinus*
L. casei	*Lacticaseibacillus casei*
S. salivarius	*Streptococcus salivarius*
P. vulgaris	*Proteus vulgaris*

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Conflict of Interest

The authors declare no conflict of interest.

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