ISSN 1070-3284, Russian Journal of Coordination Chemistry, 2021, Vol. 47, No. 12, pp. 861–880. © Pleiades Publishing, Ltd., 2021.

# Recent Studies on the Antimicrobial Activity of Copper Complexes

**O. A. Zalevskaya[a], * and Y. A. Gur'eva[a]**

[a] *Institute of Chemistry, Komi Scientific Centre, Ural Branch of the Russian Academy of Sciences, Syktyvkar, Russia*

**e-mail: zalevskayaoa@rambler.ru*

Received April 5, 2021; revised June 23, 2021; accepted June 24, 2021

**Abstract**—The analysis of publications in 2020, devoted to the synthesis of copper(II) complexes and the study of their antimicrobial properties, indicates that this area of medicinal chemistry is promising. Organic compounds of various classes were studied as starting ligands. First of all, these are N-donor imines, amines, heterocyclic compounds, as well as N,O-donor ligands and sulfur-containing ligands. In most works, the fact of a higher biological activity of the metal complex in comparison with the corresponding ligand was established. Evaluating the influence of the nature of the metal on the antimicrobial activity of the metal complex, the authors most often come to the conclusion that it is copper(II) complexes that are the most effective inhibitors of the growth of pathogenic bacteria. The scale of the studies presented indicates a high interest in this group of metal complexes, and the results indicate good prospects for using copper complexes as antimicrobial drugs.

**Keywords:** copper(II) complexes, organic ligands, antimicrobial activity

**DOI:** 10.1134/S1070328421120046

## INTRODUCTION

Reviews [1–5] devoted to the latest advances and prospects for the use of metal complex compounds as potential therapeutic agents are being actively published and indicate the increased interest of researchers in this group of three-dimensional scaffolds. An analysis of the results of screening 906 metal-containing compounds tested for antimicrobial activity within the framework of the international project Community for Open Antimicrobial Drug Discovery has been published [1]. The data obtained indicate that metal-containing compounds have a significantly higher efficiency (9.9%) compared to purely organic molecules (0.9%). Analytical work [2] gives an idea of the study of the antimicrobial activity of transition metals complexes over the past 5 years. Unfortunately, this work is superficial. For example, only three examples are given for copper complexes, although copper compounds occupy a worthy place in this series, as evidenced by previously published thematic reviews [6, 7].

The interest of researchers in complex copper compounds is associated with the fact that copper is a vital metal that is a part of many vitamins, hormones, enzymes, respiratory pigments and is involved in metabolic processes, in tissue respiration and in other biochemical processes [8]. Both an excess and a lack of copper can lead to significant disruptions in the viability of organisms and the development of diseases. The works [9, 10] present evidence of such adverse effects and it is emphasized that the level of copper in certain bioassays can serve as a marker in medical research.

The analysis of publications in 2020, devoted to the synthesis of various types copper complexes and the study of their antimicrobial properties, indicates that this area of medicinal chemistry is promising. Organic compounds of various classes were studied as starting ligands. First of all, these are N-donor imines, amines, heterocyclic compounds, as well as ligands of the salen type and sulfur-containing ligands. In most works, the fact of a higher biological activity of the metal complex in comparison with the corresponding ligand was established. Evaluating the influence of the nature of the metal on the antimicrobial activity of the metal complex, the authors most often come to the conclusion that it is copper(II) compounds that are the most effective inhibitors of the growth of pathogenic bacteria.

Authors of the review [6] "Copper complexes as therapeutic agents" substantiated the pharmacological interest of researchers in this group of metal complexes. Our analytical work continues and develops

this topic. In this article, we offer an overview of the works of 2020, which describe studies of the antimicrobial properties of complex copper(II) compounds. The list of the studied microbial targets is very extensive. For a comparative analysis, we made a sample of results for Gram-positive bacteria—*Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*), Gram-negative bacteria—*Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), and a fungus—*Candida albicans* (*C. albicans*), since it is these objects that are most often encountered in the works under discussion (see Table 1). We do not analyze the synthetic part of the research, which is of independent interest. It can only be noted that the complexation reaction, the interaction of the organic ligand with the copper(II) ion, as a rule, proceeds easily under mild conditions. This fact is an additional bonus from the standpoint of the practical implementation of the results obtained.

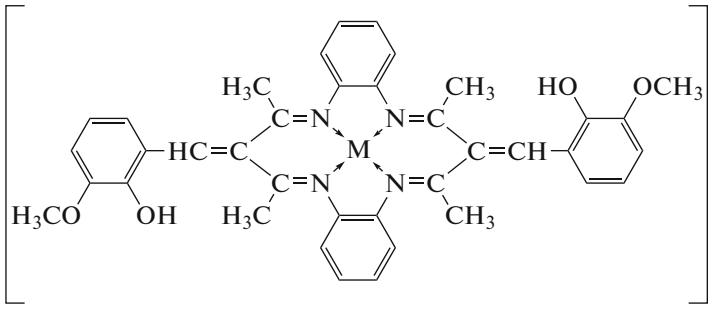
## N-DONOR LIGANDS

Metal complexes formed by chelating N,N-donor ligands are usually ionic. Various metal complexes **1a**–**1e** have been synthesized from macrocyclic Schiff base [11]. The in vitro antibacterial activity of **1a**–**1e** and parent ligand $L^1$ was investigated using *B. subtilis*, *E. coli*, *S. aureus* and *Salmonella typhimurium* (*S. typhimurium*) by the well diffusion method. The observed results indicate that the metal complexes exhibit slightly higher antimicrobial activity than free ligand. With regard to the selected line of pathogens, the minimal inhibitory concentration (MIC) for the free ligand $L^1$ is 45–65 mg/mL, while for metal complexes **1a**–**1e** these values are not higher than 30 mg/mL. To explain this fact, the authors [11] refer to Tweedy's Chelation theory [12], according to which coordination decreases the polarity of the central ion, which generally increases the lipophilicity of the system and facilitates penetration through the lipid layer of the membrane. Copper complex **1a** exhibited higher activity against *B. subtilis*, *E. coli* compared to nickel (**1b**), cobalt (**1c**), manganese (**1e**) and zinc (**1e**) complexes. It can be especially noted that the activity of the copper complex **1a** against Gram-negative *E. coli* (MIC 10 mg/mL) was higher than the activity of the antibiotic streptomycin (MIC 14 mg/mL). Equally high is the antifungal activity of this compound **1a** against *C. albicans* (MIC 10 mg/mL), which is comparable to the activity of nystatin as the standard (MIC 12 mg/mL).

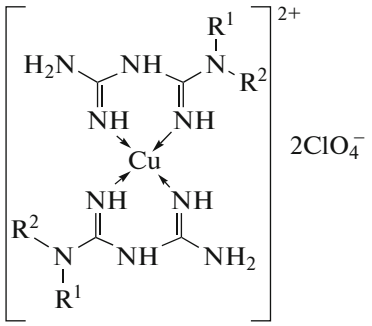
Mononuclear copper complexes **2**–**4** of metformin type biguanidine ligands $L^2$–$L^4$ were prepared in one pot reaction [13]. The corresponding ligands were formed in situ as a result of the reaction of dicyandiamide with the corresponding amines in the presence of $Cu^{2+}$ ions. It is interesting to note that, in the absence of a copper salt, this reaction does not occur and free ligands are not formed. The complexes **2** and **3** showed considerable antibacterial activity towards *E. coli*, *S. typhimurium*, *S. aureus* and *Bacillus cereus* (*B. cereus*) when compared to those standart antibiotics (amikacin and gentamicin). Complex **2** exhibits better activity towards *E. coli* than standart antibiotic gentamicin under same experimental conditions. Complex **4** containing a bulky aromatic substituent is not effective against *E. coli* and *B. cereus* at the concentration studied (MIC 12.5 mg/mL). Moreover, the complexes **2**–**4** were found to be inactive towards *C. albicans* at 12.5 mg/mL concentration.

Bidentate Schiff base ligand 2-((1HBenzo[d]imidazole-4ylimmino)methylphenol ($L^5$) was used [14] as ligand to obtain complexes of copper (**5a**), cobalt (**5b**), and zinc (**5c**). The proposed structure of complex compounds **5a**–**5c** is questionable. There is reason to believe that the ligand $L^5$ is monodentately coordinated with the metal ion. Evaluation of antibacterial activity against *S. aureus*, *E. coli*, *P. aeruginosa* showed that all metal complexes are active inhibitors of the growth of pathogenic bacteria. The diameter of the zone of inhibition (not less than 10 mm) is comparable to the values observed for the antibiotic amikacin (15–20 mm). In this case, the ligand $L^5$ in all cases has a lower activity. High antifungal activity of all metal complexes **5a**–**5c** against the *C. albicans* strain was noted, significantly exceeding the effect of nystatin. It should be especially noted that the copper complex **5a** occupies a leading position in all tests. The authors [14] correlate the high antimicrobial activity of the copper complex **5a** with the established ability to form bonds with DNA.

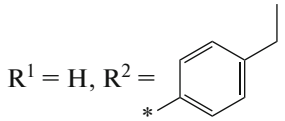
*N*,*N*,*N*',*N*'-Tetramethylethylenediamine (Tmen, $HL^6$) and carboxylate ions were used [15, 16] as ligands for the synthesis of copper complexes **6a, 6b**. This group of Pakistani researchers actively publishes work on the study of structure and antibacterial activity of complexes of this composition. The results obtained confirm once again the fact of a higher bioactivity of metal complexes in comparison with free ligands. The results [15] of antibacterial activities of the complex 6a were obtained for *Bacillus spizizenii* (*B. spizizenii*), *Enterobacter aerogenes* (*E. aerogenes*), *E. coli*, *Klebsiella pneumonia* (*K. pneumonia*), *P. aeruginosa*, *Salmonella enteric* (*S. enteric*), *S. aureus* with MIC values of 10, 250, 250, 100, 250, and 25 μg/mL. The highest activity was observed in relation to *B. spizizenii* and *S. aureus*. The synthesized complex **6a** showed no antifungal activity against *Aspergillus niger* (*A. niger*). But the complex **6a** has antimicrobial activity higher than both ligands and the copper(II) salt.



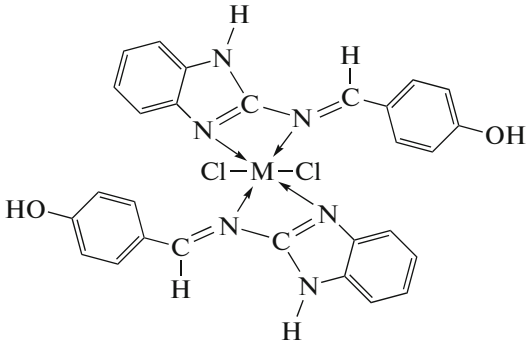
M = Cu (**1a**), Ni (**1b**), Co (**1c**), Mn (**1d**), Zn (**1e**)



$R^1 = R^2 = C_2H_5$ (**2**), $R^1 = R^2 = n\text{-}C_3H_7$ (**3**)



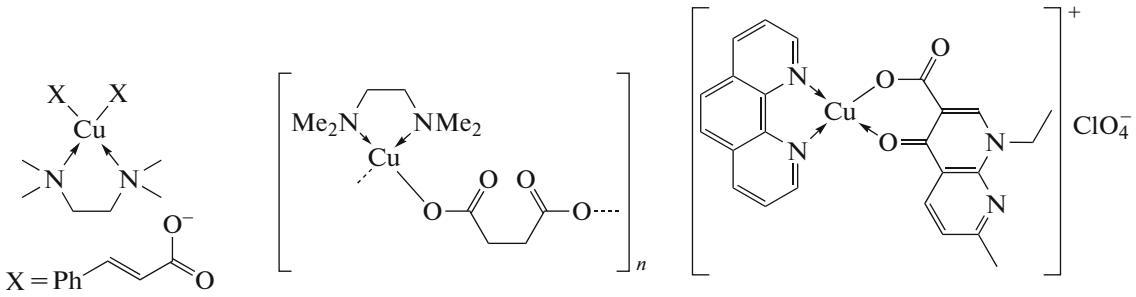
(**4**)



M = Cu (**5a**), Co (**5b**), Zn (**5c**)

The use of succinates as carboxylate ions makes it possible to obtain coordination polymers, for example, compound **6b** [16]. The antibacterial activity of **6b** in DMSO was measured for three different concentrations (1000, 500 and 250 μg/mL) against *B. spizizenii*, *E. coli*, *K. pneumonia*, and *S. aureus*. The fungal strain used was *A. niger*. Complex **6b** was active against *E. coli* showing MIC < 250 mg/mL. The rest of the strains, *B. spizizenii*, *K. pneumonia*, and *S. aureus*, and the fungal strain *A. niger* showed no activity. For comparison, the authors [16] references to their previous works [17–19], in which study of copper(II)-Tmen-carboxylates complexes. In general, it can be concluded that coordination polymer **6b** is significantly inferior to mononuclear analogs (for example, **6a**) in antimicrobial activity.

Derivatives of 2,2'-bipyridine (Bipy) and 1,10-phenanthroline (Phen) are good chelating ligands for the synthesis of metal complexes, the antibacterial properties of which are being actively studied [20–23]. The work of Turkish researchers [20] describes the synthesis and study of antibacterial properties mix-ligand coordination compound **7** next composition—$[Cu(L^7)(Phen)(H_2O)]\cdot Phen\cdot ClO_4\cdot 2H_2O$. As a soligand, nalidixic acid ($HL^7$)—an antibacterial drug belonging to the group of quinolones—was used. The authors pay special attention to assessing the change in the antimicrobial activity of this drug as a result of its coordination with the metal. For this purpose, not only classical studies have been carried out, but also computer modeling (Structure—activity relationship, Molecular docking calculation) has been carried out. The complex **7** was compared with nalidixic acid and with similar structures. The new compound **7** was found to have higher interactive than the nalidixic acid. Theoretical calculations were confirmed in the results of experimental studies. Antimicrobial activities were tested against two Gram-positive bacteria (*B. subtilis* and *S. aureus*), three Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumonia*) and a fungus (*C. albicans*) by using microdilution method. Nalidixic acid and complex **7** did not differ much in terms of antibacterial activity, but it observed a great improvement in antifungal activity in the compound **7** that was not found in the nalidixic acid.

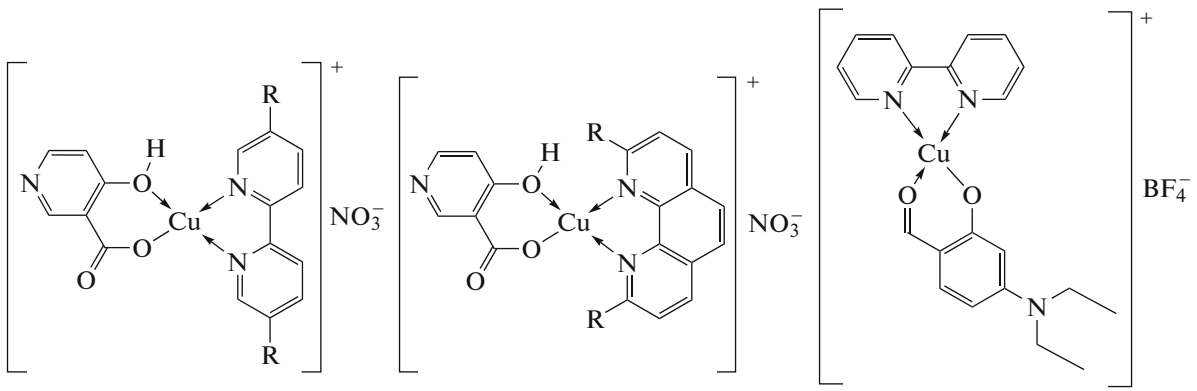


(6a) (6b) (7)

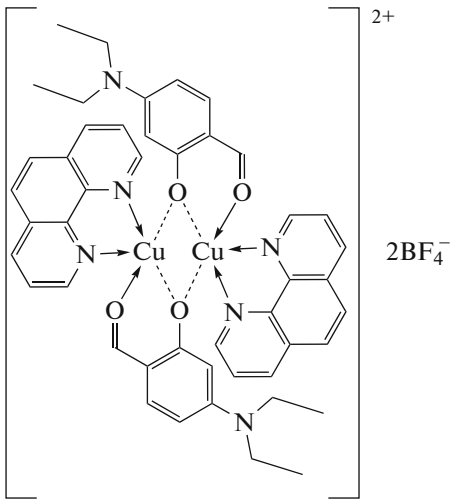
The authors [21] describe the synthesis of four mixed ligand copper complexes **8a**–**8d** containing aromatic diimines as primary ligands while 4-hydroxynicotinic acid ($HL^8$) as secondary ligand. The antimicrobial activity of all these complexes are more active compare to free ligands ($HL^8$ and aromatic diimines) against bacteria *B. subtilis*, *S. aureus* and *E. coli*. The antibiotic amikacin showed much lower activity compared to metal complexes **8a**–**8d**. On the other hand, found that $HL^8$ and all the metal complexes **8a**–**8d** showed no fungal growth inhibition.

The work of Serbian scientists [22] can serve as a model of research in which tasks are very logically and competently planned and the results obtained are discussed. Complexes **9a** and **9b** were obtained in the reaction of $Cu(BF_4)_2 \cdot 6H_2O$, deprotonated 4-(diethylamino)-2-hydroxybenzaldehyde ligand ($HL^9$) and diimine (Bipy or Phen). Copper complexes **9a** and **9b** demonstrated significantly stronger antibacterial activities than the parent ligands (diimines and $HL^9$). Correspondingly, **9b** is the most active of all examined compounds. The activity of this complex against all tested bacterial strains is comparable to the activity of the standard antibiotic amikacin. Comparing to **9a** and **9b**, starting Cu(II) salt and ligand $HL^9$ have lower activity against all bacterial strains, so activity significantly increases with their coordination. Unlike increasing antibacterial activity of **9a** and **9b** regarding all coordinated ligands, antifungal activities showed the opposite trend. Although **9b** has antifungal activity better than fluconazole, its matching diimine ligand (Phen), showed extremely good antifungal activity. In comparison with fluconazole, Cu(II) salt, ligand $HL^9$, as well as **9a**, showed similar activity against fungal strains.

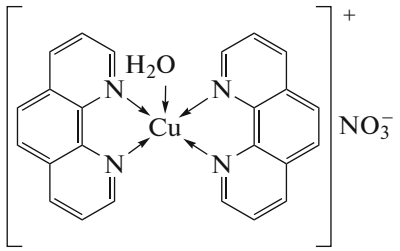
For comparison [23] it should be noted that the homoleptic copper complex **10** with Phen ligands showed a very low antimicrobial activity in comparison with the used standards. It should be noted that in this work there is no comparative analysis of the initial ligands and the corresponding complexes, despite the fact that the authors stated in the introduction about examples of the bioactivation of ligands due to complexation.



R = H (**8a**), $CH_3$ (**8b**) R = H (**8c**), $CH_3$ (**8d**) (**9a**)



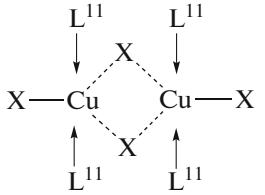

(**9b**)



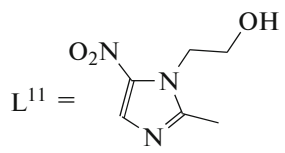

(**10**)

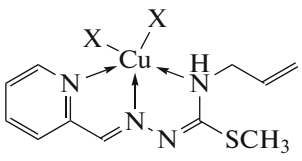
A number of researchers use compounds from the group of clinical pharmaceuticals as ligands, hoping to enhance the bioactivity of the latter as a result of coordination with the metal. For example, copper complexes with metronidazole (MET, $L^{11}$) were studied [23, 24]. MET is one of the FDA-approved antibiotic drugs which has been known and widely used in clinical practice. The parent ligands and the synthesized complex **11a** were examined [24] for their in vitro antimicrobial activity against three Gram-negative, Gram-positive bacteria and a fungus *C. albicans*. In most cases the complex **11a** showed an appreciable antimicrobial activity against *K. pneumonia*, *S. typhimurium*, *E. coli* when compared with trichloroacetic acid (TCA). The synthesized complex **11a** was more potent against *C. albicans* than the MET and the TCA. The authors [23] describe a copper complex of a similar composition with chloride ions (**11b**). A very low antimicrobial activity of the latter was established. In contrast to the trichloroacetate analogue (**11a**), compound **11b** is inactive against the *C. albican*s (MIC 31.1 μg/mL, for nystatin—1.56 μg/mL). In the case of complex **11a**, the main contribution to the antifungal activity is apparently made by the trichloroacetate ligand. It follows from this that when assessing the biological activity of a complex compound, all its constituent components should be taken into account.

N-Donor chelating ligands were used to synthesize metal complexes [25, 26]. New copper(II), zinc(II), nickel(II) and cobalt(III) complexes were obtained with isothiosemicarbazone ligand ($L^{12}$) [25]. For example, three copper complexes **12a**–**12c** are selected. The ligand and the complexes were tested for their antimicrobial activity against *S. aureus*, *E. coli*, *K. pneumonia* and *C. albicans*. The most vulnerable to the studied substances was *S. aureus*. In this case, the values of MIC and MBC (minimum bactericide concentration) vary in the range of concentrations 0.7–3 μg/mL, which indicate the high activity of synthesized compounds. These values are several times higher than activity of furacillinum that is used in medical practice. It is interesting to note that the ionic complex **12c** has a noticeably lower activity than the neutral complexes **12a** and **12b**. In the latter case, the nature of the halide (chloride or bromide) is irrelevant.

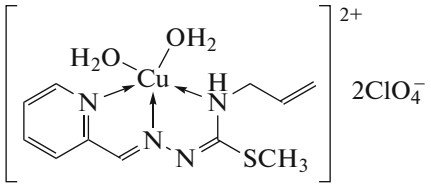


X = $CCl_3COO^-$ (**11a**), $Cl^-$(**11b**)



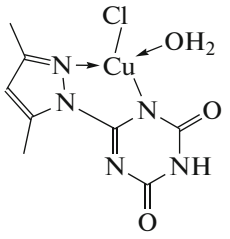


X = Cl (**12a**), Br (**12b**)

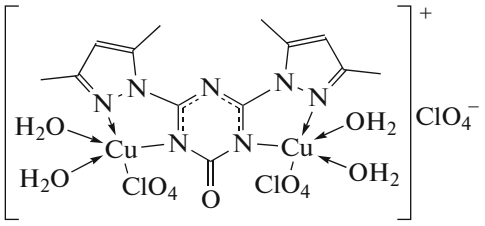



(**12c**)

Two unexpected one-dimensional coordination polymers of triazine-based ligands were synthesized by Cu(II)-mediated hydrolysis of the 2,4-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-methoxy-1,3,5-triazine pincer ligand ($HL^{13}$) [26]. Structural units of coordination polymers can be represented by formulas **13a** and **13b**. Antimicrobial activity study results showed that binuclear complex **13b** has a higher antibacterial activity against *E. coli*, *B. subtilis,* and *B. cereus* as well as against the fungus *C. albicans* than mononuclear analogue **13a**. The bioactivity results of these complexes were compared with a selected set of common antibiotics (amoxicillin, tetracycline, and ampicillin). Interestingly, complex **13b** showed better activity against *E. coli*, *B. subtilis,* and *C. albicans* compared with these antibiotics. For all other remaining microorganisms, the results are generally comparable for the copper complexes and antibiotics.



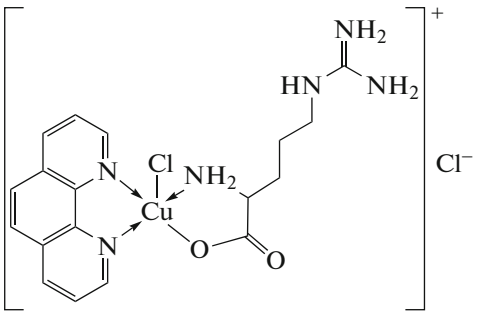
**(13a)**



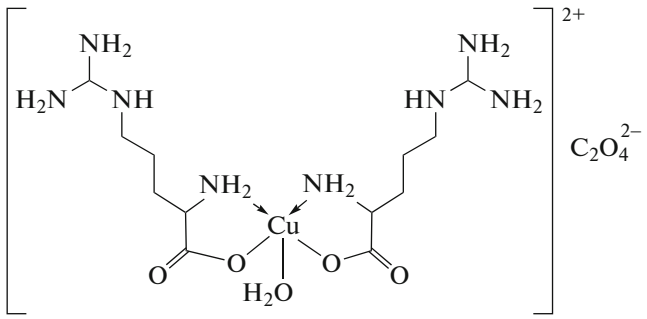
**(13b)**

## N,O-DONOR LIGANDS

Publication [27] is one of works by Polish researchers devoted to study the structure and biological activity of copper complexes containing amino acids as ligands. The idea of introducing natural origin structural groups with known biological activity into the complex is very productive. Antimicrobial activity of copper arginate complexes **14a**, **14b** was confirmed [27]. These coordination compounds contain L-arginine ($HL^{14}$) as a co-ligand. Among ten microorganisms tested in this study all strains were sensitive to complexes **14a** and **14b** with MIC ≤ 15 μM. Both complexes proved to have a significant inhibitory efficacy against Gram-positive strains at concentration below 5 μM. It is interesting to note that the mixed ligand complex **14a** exhibits higher antibacterial activity. Gram-negative strains were more resistant to both complexes.



**(14a)**

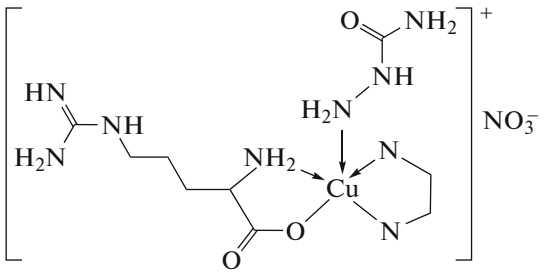


**(14b)**

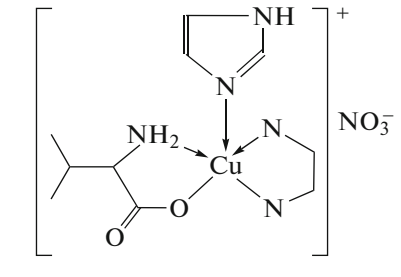
Mixed ligand complexes of this type containing amino acid and heterocyclic bases have been investigated in the works of Indian scientists [28, 29]. Two copper arginate complexes (**14c** and **14d**) have been synthesized [28], which were found to exhibit considerable activity against bacteria (*B. subtilis, S. aureus* and *P. aeruginosa*) and fungus (*A. niger, M. specie*). Ternary copper complexes **15a** and **15b** containing L-valine ($HL^{15}$) as a co-ligand exhibit high antibacterial activity against *S. aureus,* comparable to the action of a standard antibiotic [29]. The authors [28, 29] investigated the interaction of metal complexes **14c**, **14d** and **15a**, **15b** with DNA and found that the mixed ligand complexes containing amino acid and heterocyclic bases

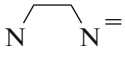
show a unique DNA binding property, that conform with good antibacterial and antifungal activities.

For the synthesis of copper (**16a**) and cobalt (**16b**) complexes, the authors [30] used the Schiff base ligand ($HL^{16}$) derived from the condensation of citral with L-valine. The results revealed that the Schiff base ligand exhibited the poor antimicrobial activity against *E. coli* and *C. albicans* except for *S. aureus*. Cobalt complex **16b** seem to be more active against *E. coli* organisms in comparison to copper complex **16a**, which exhibits higher activity than uncomplexed ligand.

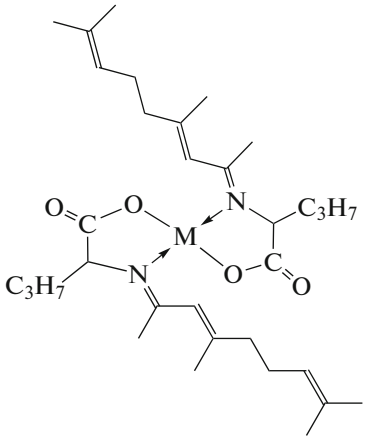


= phen (**14c**), bipy (**14d**)





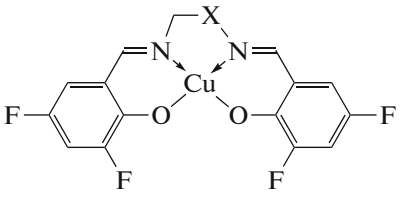
= phen (**15a**), bipy (**15b**)



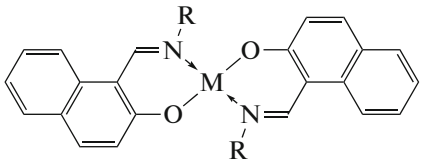
M = Cu (**16a**), Co (**16b**)

The N,O-donor ligands include the salen type ligands studied in a number of works [31–34]. Three mononuclear copper complexes **17**–**19** with bis-Schiff base ligands $HL^{17}$–$HL^{19}$ were prepared and structurally characterized [31]. Regardless of the structure of the bridge fragment, the complexes have an identical structure. The donor atoms of the square planar coordination comprise two imino nitrogen and two phenolate oxygen of the ligands $HL^{17}$–$HL^{19}$. The results of the study of antimicrobial activity show that the complexes **17**–**19** have broad antimicrobial activities against all the tested organisms. The complexes **17**–**19** have higher activities against *Streptococcus pyogenes* (*S. pyogenes*), *Streptococcus agalactiae* (*S. agalactiae*), and *S. aureus* when compared to the penicillin. In general, complex **19**, characterized by the presence of an additional hydrophilic OH group, has better activities than the other two. Complex **19** has the most active against *S. agalactiae* with the MIC value of 8 μg/mL.

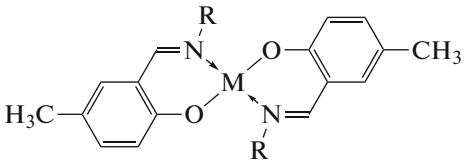
A series of bivalent metal complexes (**20a**–**20c** and **21a**–**21c**) with Schiff base ligands 1-(5-(4-fluorophenyl)isoxazol-3-ylimino)methyl)napthalen-2-ol ($HL^{20}$) and 2-(5-(4-fluorophenyl)isoxazol-3-ylimino)methyl)-4-methylphenol ($HL^{21}$) have been synthesized [32]. The antimicrobial screening results displayed that the Schiff base ligands $HL^{20}$ and $HL^{21}$ were moderately active against bacterial and fungal strains whereas the corresponding metal complexes **20a**–**20c** and **21a**–**21c** show higher activity than free Schiff base ligands. From the above results it is concluded that, among all, copper complexes **20c** and **21c** show highest potential activity against mentioned bacterial and fungal species.



X = $CH_2$ (**17**), $(CH_2)_2$ (**18**), $CH(OH)CH_2$ (**19**)

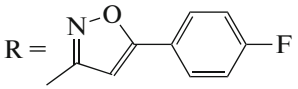


(**20a**)–(**20c**)



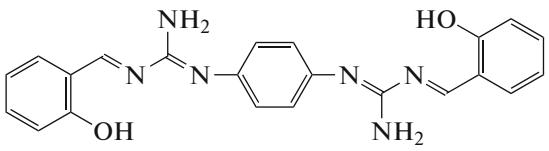
(**21a**)–(**21c**)

M = Co (**20a**, **21a**), Ni (**20b**, **21b**), Cu (**20c**, **21c**)

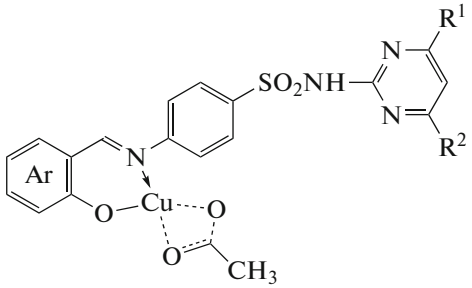
R = 

Transition metal complexes **22a**–**22d** of a multidentate Schiff base ligand $H_2L^{22}$ containing guanidine moiety have been investigated [33]. In particular, binuclear complexes of the following composition were obtained: $[(L^{22})Cu_2(OAc)_2(H_2O)_6]\cdot 2H_2O$ (**22a**); $[(L^{22})Cu_2(Cl)_2(H_2O)_6]$ (**22b**); $[(H_2L^{22})Cu_2(SO_4)_2(H_2O)_2]\cdot 3H_2O$ (**22c**); $[(L^{22})Cu_2(NO_3)_2(H_2O)_6]\cdot 2H_2O$ (**22d**). Unfortunately, the authors do not provide convincing evidence of the proposed structure of the obtained complex compounds. The results indicated that the metal complexes **22a**–**22d** had a more noteworthy effect than the ligand against the test organisms. It has been detected that ligand $H_2L^{22}$ showed direct anti-bacterial and anti-fungal effects in comparison to the standard drugs (neomycin or cycloheximide) with clear zones values of 13, 14, 15, and 25 mm for *S. aureus*, *P. aeruginosa*, *C. albicans* and *A. niger*, respectively. Complexes **22a**–**22d** showed a higher hostile effect to Gram-negative bacteria (*P. aeruginosa*) in comparison to the ligand (13 mm) with clear zone values of 15, 18, 17, 23 mm, respectively. Moreover, complexes **22a** and **22b** were more hostile to *S. aureus* than the ligand with clear zone values of 18, 15 mm, respectively. Additionally, complexes **22a**–**22c** had higher anti-fungal effects against the yeast *C. albicans* than the ligand $H_2L^{22}$ (15 mm) with inhibition zone values of 20, 22, 23, mm. The results obtained indicate that not only the organic ligand, but also the nature of the mineral anion is of great importance from the point of view of biological activity. For example, the nitrate complex **22d** was unexpectedly inactive against *S. aureus*, but most active against *P. aeruginosa*.

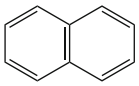
A series of nanometer-sized spherical sulfonamide imine ligands $HL^{23}$–$HL^{27}$ and their copper and zinc complexes were synthesized and fully characterized [34]. The composition of copper complexes **23**–**27** corresponds to the general formula $[Cu(L)(OAc)]\cdot nH_2O$. Copper complexes exhibited a higher potent activity than zinc analogues. Noteworthy, inhibition activity of $[Cu(L^{25})(OAc)]$ complex is higher than that of the standard ampicillin. $[Cu(L^{24})(OAc)]$ complex displayed a similar activity of the standard bactericides and fungicides in use. The $[Cu(L^{25})(OAc)]$ complex showed high potency against *Aspergillus fumigates* (*A. fumigates*) and it even displayed higher activity than amphotericin B. The $[Cu(L^{24})(OAc)]$ possessed more potent activity than its parent ligand and it displayed similar activity like the fungicide in use. In this work [34], it was established once again that metal chelates have higher activity than free ligands.



$H_2L^{22}$



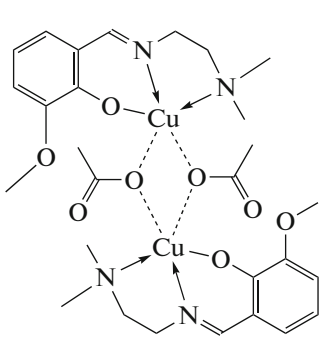
Ar =  $R_1 = R_2 = CH_3$ (**23**); $R_1 = H$, $R_2 = CH_3$ (**24**)

Ar =  $R_1 = R_2 = CH_3$ (**25**); $R_1 = H$, $R_2 = CH_3$ (**26**); $R_1 = R_2 = H$ (**27**)

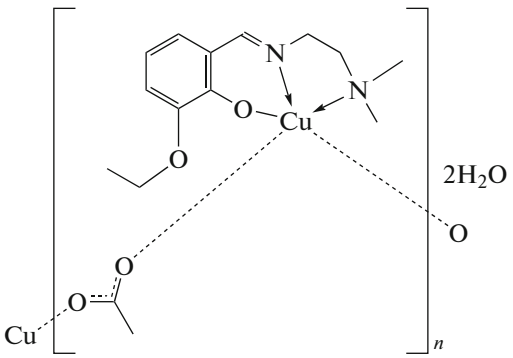
## TRIDENTATE N,N,O-DONOR LIGANDS

Copper complexes **28** and **29** of the two new Schiff base ligands ($HL^{28}$ and $HL^{29}$) derived from 2-hydroxy-3-methoxy benzaldehyde and 3-ethoxy-2-hydroxy-benzaldeyhde with *N*,*N*'-dimethylethane-1,2-diamine have been prepared [35]. It is interesting to note that small structural changes in the ligand (replacement of a methyl group by an ethyl group in the aromatic fragment) lead to significant changes in the stoichiometry of the compounds formed: compound **28** is a binuclear complex with acetate bridging ligands, and **29** is a coordination polymer. It was found that complexes **28** and **29** had anti-microbial activity on Gram-negative bacteria *E. coli* and Gram-positive bacteria *S. aureus*. This antimicrobial activity was stronger than that of Neomycin on both bacterial strains. Complexes **28** and **29** exerted a light responsive nature which makes them good candidates for photodynamic therapy applications.

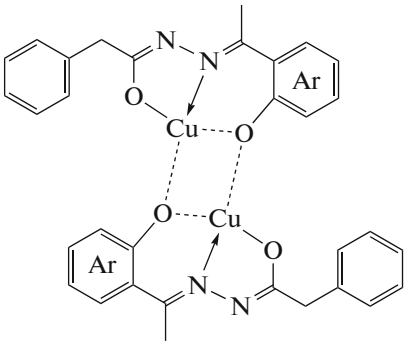
Thermal reactions of the Cu(II) ions with the two Schiff base ligands [*N*'-(1-(2-hydroxyphenyl)ethylidene))-2-phenylacetohydrazide] ($HL^{30}$) and [*N*'-((1-hydroxynaphthalen-2-yl)methylene)-2-phenylacetohydrazide] ($HL^{31}$) resulted in formation of the binuclear complexes **30** and **31** [36]. The two ligands $HL^{30}$ and $HL^{31}$ showed no activity towards either the bacteria or the fungi. On the other hand, the results indicated high antimicrobial activities for the complexes **30**, **31** and were found to be comparable with that of standards.



(**28**)



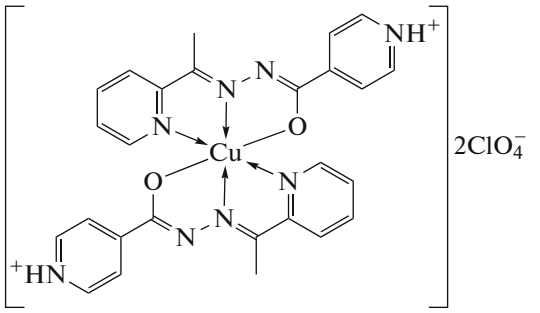
(**29**)



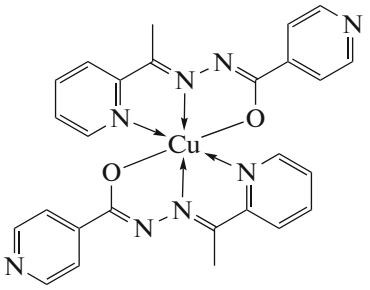
Ar = Ph (**30**), Naf (**31**)

The complexes **32a** and **32b** were readily synthesized by reaction of the *N*-(1-(pyridin-2-yl)-ethylidene)isonicotinohydrazide ($HL^{32}$) with copper perchlorate and copper acetate in ethanol at ambient temperature [37]. During the formation of complex **32a** strong perchloric acid is released, that leads to protonation of the pyridinic nitrogen of the ligand and leads to the formation of cationic complex. Whereas in

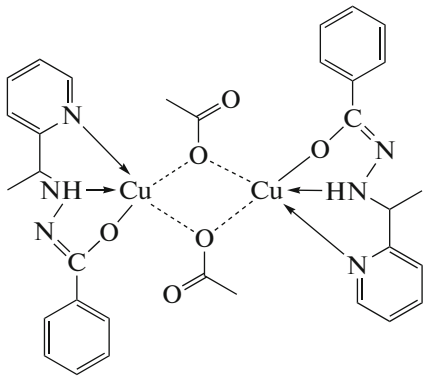
case of complex **32b** weak acetic acid is released during the reaction, protonation doesn't occur, molecular complex forms. A comparative study of MIC values of the hydrazone $HL^{32}$ and the two copper complexes (**32a**, **32b**) indicates that complexes have similar antimicrobial activities, and have higher antibacterial and antifungi activities against *S. aureus*, *E. coli*, and *C. albicans* when compared to the free hydrazone.



**(32a)**



**(32b)**



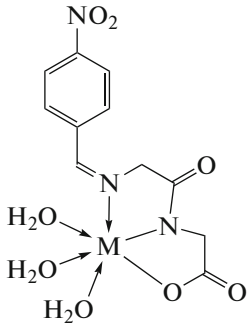
**(33)**

The work [38] reports a joint experimental and theoretical study of a novel copper complex $[CuL^{33}(\mu\text{-}CH_3COO)]_2$ (**33**), based on 2-acetylpyridine-benzoylhydrazone ligand ($HL^{33}$). The complex **33** was more active than the ligand $HL^{33}$, against the tested Gram-positive and Gram-negative bacteria. The complex **33** was inactive against *E. aerogenes*, while showed significant activity against the other bacteria, with the best result against *S. epidermidis*. The tested compounds showed better activity against the Gram-positive bacteria than the Gram-negative bacteria, possibly due the major complexity of the cell wall of the Gram-negative strains, which can difficult the action of the tested compounds in the intracellular environment. The hydrazone and their copper complex demonstrated significant antifungal activity against *C. albicans* and *Cryptococcus neoformans* (*C. neoformans*).

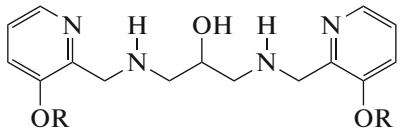
Water soluble transition metal (Cu(II), Co(II), Ni(II), and Zn(II)) complexes **34a**–**34d** with N,N,O-donor ligand $H_2L^{34}$ obtained from glycylglycine and 4-nitrobenzaldehyde were synthesized [39]. Generally, it has been observed that metal chelates **34a**–**34d** has more antimicrobial activity than the free ligand $H_2L^{34}$. All the complexes **34a**–**34d** exhibited appreciable antimicrobial activity against the tested microorganisms. Among the metal chelates copper complex **34a** showed a remarkable activity, especially against the Gram-negative bacteria such as *E. coli*, comparable to the standard drug ciprofloxacin. DNA cleavage experiment was carried out using gelelectrophoresis technique, where the mechanism is migration of deoxyribonucleic acid (DNA) fragments with respect to applied electric potential. *E. coli* DNA was used for this study, with ligand $H_2L^{34}$ and its metal complexes **34a**–**34d** in the absence of an oxidant. DNA cleavage studies show that the copper complex **34a** has completely cleaved the DNA, which is in good agreement with the high antibacterial activity of this compound.

A macromolecular approach to the design of a copper-containing antimicrobial drug was used [40]. Immobilization of an active substance on a polymer matrix has a number of advantages, one of which is the prolongation of the drug's action in a biological environment. The spherical, water-dispersed microgels

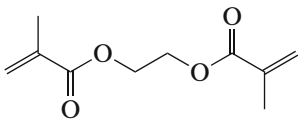
(P) are synthesized from miniemulsions that are obtained by ultra-sheering of monomer mixtures in aqueous solutions. A pre-polymerization mixture typically consists of ethylene glycol dimethacrylate (EGDMA) as a cross-linking agent, butyl acrylate (BA) as a monomer, and $L^{35}$ as a pentadentate backbone ligand. The immobilized ligand is usually transformed in situ into a binuclear metal complex by addition of $Cu(OAc)_2$ prior to polymerization. The systematic study [40] reveals that *S. aureus* is susceptible to the microgels, while common commercial agents are found intermediate or resistant. In particular, a microgel with 60 mol % of cross-linking ($Cu_2L^{35}/P_{60\%}$) shows intriguing bactericidal activity at 1 μg/mL, while vancomycin requires a 4-fold higher dose, i.e., 4 μg/mL, for the same effect. The MIC of $Cu_2L^{35}/P_{60\%}$ was determined as low as 0.64 μg/mL. Control experiments reveal a 617-fold increase in antimicrobial activity when comparing a low molecular weight binuclear complex $Cu_2L^{35}$ to its microgel analogue $Cu_2L^{35}/P_{60\%}$.



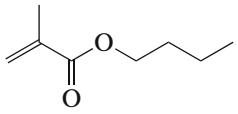
M = Cu (**34a**), Co (**34b**), Ni (**34c**), Zn (**34d**)



R = (L[35])



EGDMA



BA

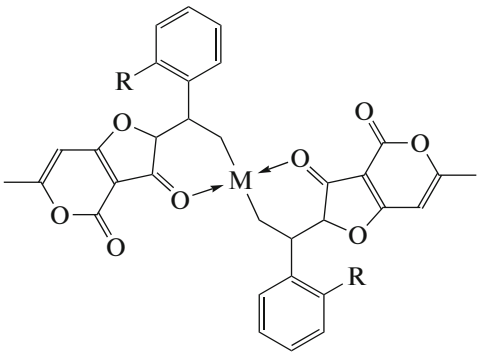
## O,O-DONOR LIGANDS

Four new metal complex (**36a**, **36b** and **37a**, **37b**) derivatives of two new ligands 2-(hydroxy(phenyl)-6-methyl-2H-furo[3,2-c]pyran-3,4-dione ($HL^{36}$) and 2-(hydroxyl(2-hydroxyphenyl)-6-methyl-2H-furo[3,2-c]pyran-3,4-dione ($HL^{37}$) with the metal ions Mn(II) and Cu(II) have been successfully prepared in alcoholic medium [41]. The copper complex **36a** showed an important activity than that of the ligand $HL^{36}$ namely an excellent antibacterial activity against Gram-positive bacteria (*S. aureus*, group *D Streptococcus*) and a moderate activity against Gram-negative bacteria (*E. coli*, *K. pneumonia*). The high resistance of Gram-positive bacteria is related to the complexity of the cell wall of these microorganisms which contains a double membrane, unlike the simple membrane structure of Gram-negative bacteria. The copper (**37a**) and manganese (**37b**) complexes exhibit activity relative to that of ligand $HL^{37}$ with respect to the bacteria tested. It should be noted that the Mn and Cu complexes have a good antibacterial activity particular to the bacterium group *D Streptococcus*. In general, the copper (**36a**) and manganese complexes (**36b**) derived from the $HL^{36}$ ligand are more active than the $HL^{37}$ ligand complexes (**37a** and **37b**). The authors [41] note that this antimicrobial behavior is related to the electronic effect of the substituents. It was found that the ligands and their metallic complexes exhibit excellent antifungal activity against *C. albicans* and *Candida tropicalis* (*C. tropicalis*). The diameters of the inhibition zones 40 mm for the four complexes (**36a**, **36b** and **37a**, **37b**). For comparison the diameters of the inhibition zones of ketokonazole used as standard reference for *C. albicans* and for *C. tropicalis* are respectively 33 and 35 mm. In parallel, the synthesized coordination complexes showed a clear improvement of the antifungal tests in comparison with those of the free ligands.

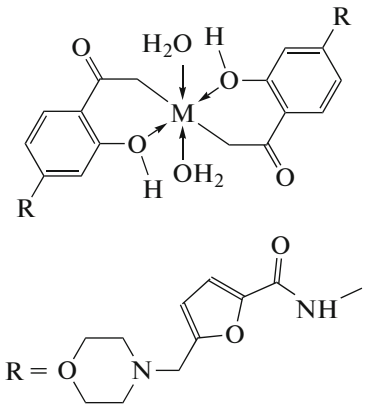
The Cu(II), Co(II), Ni(II), Mn(II) and Zn(II) metal chelates **38a**–**38e** of 2-hydroxy-4-(5-(morpholinomethyl))furan-2-carboxamido)benzoic acid ($HL^{38}$) have been prepared [42]. The free ligand and

it's complexes have been tested for their antibacterial activities against two types of human pathogenic bacteria. Out of all the compounds copper chelate is more toxic than other. The compound **38a** almost inhibit the fungi about 73%.

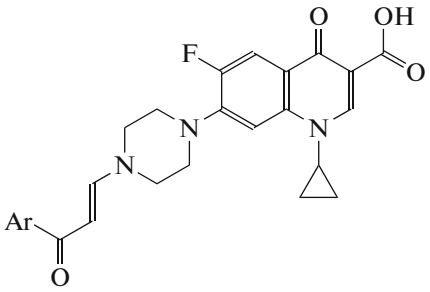
Ciprofloxacin (CF) derivatives $HL^{39}$–$HL^{44}$ used for synthesis six copper complexes **39**–**44** general composition $[Cu(L)_2(H_2O)_x]\cdot yH_2O$ [43]. CF belongs to class II of the second-generation fluoroquinolone—synthetic antibiotics that are active against both Gram-positive and Gram-negative bacteria. Copper complexes of the synthesized CF derivatives $HL^{39}$–$HL^{44}$ showed sensitivity against *S. aureus*, *E. coli*, *K. pneumonia*, and ESBL positive *K. pneumonia*. The presence of copper(II) ions enhanced the antibacterial reactivity of the derivatives, illustrating the effect of the metal ion on the properties of the ligands.



R = H, M = Cu (**36a**), Mn (**36b**);
R = OH, M = Cu (**37a**), Mn (**37b**)



M = Cu (**38a**), Ni (**38b**), Co (**38c**), Mn (**38d**), Zn (**38e**)

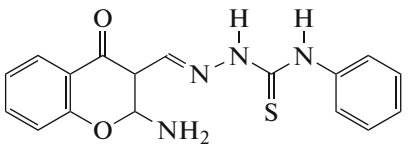


Ar = phenyl ($HL^{39}$), *p*-methylphenyl ($HL^{40}$), *p*-chlorolphenyl ($HL^{41}$), *p*-nitrophenyl ($HL^{42}$), furan ($HL^{43}$), pyrrol ($HL^{44}$)

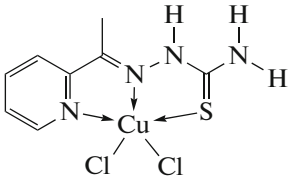
## S-DONOR LIGANDS

Sulfur-containing ligands are actively used for the synthesis of copper complexes, the antimicrobial activity of which is an established fact [44–56]. A new series of binary and ternary complexes **45a**–**45h** of monoprotic tridentate N,O,S-donor ligand, 2-[(2-aminochromon-3-yl)methylidene]-*N*-phenylhydrazine carbothioamide ($HL^{45}$), has been synthesized [57]. The authors investigate the effect of anions, and presence of auxiliary ligand on the structure and their properties. The ligand $HL^{45}$ was reacted with different salts of Cu(II) ion ($OAc^-$, $NO_3^-$, $SO_4^{2-}$ and $Cl^-$) in absence and presence of secondary ligands (8-hydroxyquinoline (8-HQ), Phen or $SCN^-$) to form binary and ternary Cu-chelates next composition: $[Cu(L^{45})(OAc)(H_2O)]\cdot H_2O$ (**45a**); $[Cu(L^{45})(CH_3OH)_3]NO_3$ (**45b**); $[Cu(HL^{45})(SO_4)]$ (**45c**); $[Cu(L^{45})Cl]$ (**45d**); $[Cu(L^{45})_2]\cdot 2H_2O$ (**45e**); $[Cu(L^{45})(SCN)]$ (**45f**); $[Cu(L^{45})(8\text{-}HQ)(H_2O)]NO_3$ (**45g**); $[Cu(L^{45})(phen)(H_2O)]NO_3$ (**45h**). The ligand $HL^{45}$ exhibits low activity against all tested pathogenic

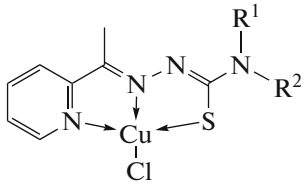
organisms. The activity of metal complexes **45a**–**45h** varies from lower to intermedate activity, except complex **45b** that has high activity towards *S. aureus*. The authors [57] note that the dipole moments may give some insight on the degree of hydrophobicity/hydrophilicity of the compounds properties. The antimicrobial study reveals that the metal complexes more active against Gram-positive than Gram-negative bacteria. Studies suggested that there is an inverse correlation between the dipole moment and the activity of the complexes against the studied bacterial and fungal species.



$HL^{45}$



**(46)**



$R^1 = H$, $R^2 = CH_3$ (**47**), $R^1 = R^2 = CH_3$ (**48**)

The synthesis and characterization of the three copper thiosemicarbazone complexes **46**–**48** are described [58]. Although the ligands $HL^{46}$–$HL^{48}$ are similar in structure, the copper complexes are not. Complex **46** contains neutral thiosemicarbazone ligand and adopts a square-pyramidal geometry, while the other compounds (**47**, **48**) contain anionic deprotonated thiosemicarbazone ligands and crystallize in square-planar geometries. The antibacterial activity of metal complexes **46**–**48** is higher than that of the corresponding ligands $HL^{46}$–$HL^{48}$. Copper complexes exhibited more antimicrobial activity to Gram-negative bacteria than Gram-positive bacteria. The authors [58] associate this result with the complexity of the cell wall structure of Gram-positive bacteria and Gram-negative bacteria. The lipid membrane facilitates the passage of any fat-soluble substance, and liposolubility is known to be an important factor in controlling antibacterial activity. The ability of complexes **46**–**48** to disrupt and increase cell membrane permeability was evaluated by using Sytox green into *S. aureus* and *E. coli* cells. Sytox green is a green nucleic acid dye that easily penetrates the damaged plasma membrane and cannot penetrate the plasma membrane of living cells. When treated with copper complexes, a significant fluorescent signal was present in *S. aureus* and *E. coli*, while the untreated control did not. The results indicate that copper complexes may destroy the integrity of bacterial cell membranes and induce the absorption of Sytox green. This result allows the authors to assume that copper complexes may initially cause instability of the outer membrane, destroying the cell membrane, leading to bacterial cell lysis.

## CONCLUSIONS

First of all, one should be note a great interest of researchers in complex copper compounds in terms of their therapeutic activity. It was this fact that prompted us to write the presented review. While working on the introduction to our personal article, we found that in 2020 alone, more than 50 papers were published, which describe the results of a study of the antimicrobial activity of copper complexes. During the preparation of the manuscript for submission a number of works [59–69] were published that were not included in the above analysis.

As can be seen from the above, complex copper compounds of various types have been studied. We classified the presented material according to the type of ligand donor centers used for the synthesis of metal complexes. For a comparative assessment of the antimicrobial activity of the described copper complexes, we made a sample of results (Table 1) for two species of Gram-positive bacteria (*S. aureus, B. subtilis*), two species of Gram-negative bacteria (*E. coli, P. aeruginosa*) and fungus (*C. albicans*). Each specific study uses its own methods of studying antibacterial activity and quantifying the results. Therefore, as a criterion for comparative assessment of the effectiveness of the antimicrobial action of the compounds, we focused on the values (the numbers are highlighted in the table in bold) that exceed the effectiveness of the standard

**Table 1.** Examples of the antimicrobial activity of metal complexes, starting ligands and standards

| Compound | Antimicrobial activity against *S. aureus* (*Sa*), *B. subtilis* (*Bs*), *E. coli* (*Ec*), *P. aeruginosa* (*Pa*), *C. albicans* (*Ca*) | | | | | | Reference |
|---|---|---|---|---|---|---|---|
| | *Sa* | *Bs* | *Ec* | *Pa* | *Ca* | units | |
| L[1] | 55 | 55 | 45 | | 65 | MIC mg/mL | 11 |
| **1a** | 20 | 15 | **10*** | | **10** | | |
| **1b** | 25 | 25 | 20 | | 15 | | |
| **1c** | 15 | 20 | 20 | | 20 | | |
| **1d** | 30 | 25 | 25 | | 25 | | |
| **1e** | 20 | 35 | 15 | | 24 | | |
| Stand** | 12 | 10 | 14 | | 12 | | |
| **2** | 12 | | **15** | | N/a*** | mm**** | 13 |
| **3** | 15 | | **12** | | N/a | | |
| **4** | 12 | | N/a | | N/a | | |
| Stand | 25 | | 10 | | N/a | | |
| L[5] | 10 | | 17 | | **25–30** | mm | 14 |
| **5a** | 18 | | **27** | | **30–35** | | |
| **5b** | 15 | | **22** | | **25–30** | | |
| **5c** | 15 | | 18 | | **25–30** | | |
| Stand | 20 | | 20 | | 15 | | |
| HL[6] | N/a | | N/a | N/a | | MIC μg/mL | 15 |
| **6a** | 25 | | 250 | 250 | | | |
| Stand | 25 | | 25 | 25 | | | |
| **6b** | N/a | | 250 | | | MIC μg/mL | 16 |
| Stand | 250 | | 250 | | | | |
| HL[7] | 4 | 1 | 2 | >128 | >128 | MIC μg/mL | 20 |
| **7** | 8 | 4 | 8 | >128 | 8 | | |
| HL[8] | 2.6 | N/a | N/a | | N/a | mm | 21 |
| **8a** | **17** | **18** | **20** | | N/a | | |
| **8b** | **10** | **11** | **11** | | N/a | | |
| **8c** | **10** | **10** | **10** | | N/a | | |
| **8d** | **18** | **17** | **19** | | N/a | | |
| Stand | 9 | 6 | 6 | | 9 | | |
| $Cu(BF_4)_2$ | 3.62 | 3.62 | 3.62 | 1.81 | 3.62 | MIC mM | 22 |
| Phen | 0.056 | 0.871 | 0.438 | 0.056 | 0.028 | | |
| Bipy | 0.256 | 8.00 | 8.00 | 0.506 | 0.256 | | |
| HL[9] | 6.47 | 6.47 | 6.47 | 3.23 | 1.62 | | |
| **9a** | 0.286 | 0.571 | 0.571 | 0.144 | 1.14 | | |
| **9b** | 0.076 | 0.076 | 0.151 | 0.019 | 1.19 | | |
| Stand | 0.019 | 0.071 | 0.085 | 0.008 | 1.022 | | |
| **10** | 125 | | 125 | 62.5 | 31.3 | MIC μg/mL | 23 |
| Stand | 0.078 | | 0.078 | 0.625 | 1.56 | | |

**Table 1.** (Contd.)

| Compound | Antimicrobial activity against *S. aureus* (*Sa*), *B. subtilis* (*Bs*), *E. coli* (*Ec*), *P. aeruginosa* (*Pa*), *C. albicans* (*Ca*) | | | | | | Reference |
|---|---|---|---|---|---|---|---|
| | *Sa* | *Bs* | *Ec* | *Pa* | *Ca* | units | |
| $L^{11}$ | 24 | | 25 | | N/a | mm | 24 |
| $CCl_3COOH$ | N/a | | N/a | | 21 | | |
| $Cu(NO_3)_2$ | 17 | | 14 | | 15 | | |
| **11a** | 15 | | 19 | | 24 | | |
| **11b** | 125 | | 62.5 | 62.5 | 31.3 | MIC | 23 |
| Stand | 0.078 | | 0.078 | 0.625 | 1.56 | μg/mL | |
| $L^{12}$ | 0.7 | | 500 | | 250 | MIC | 25 |
| **12a** | **0.7** | | 60 | | **30** | μg/mL | |
| **12b** | **0.7** | | 60 | | **30** | | |
| **12c** | **1.5** | | 60 | | **60** | | |
| Stand | 9.3 | | 18.5 | | 80 | | |
| **13a** | **1.7** | **2.5** | **3.4** | 1.7 | **2.5** | MIC | 26 |
| **13b** | **1.9** | **1.9** | **2.5** | 2.2 | **1.9** | μmol/mL | |
| Stand | 2.0 | 3.5 | 3.5 | 1.5 | 3.0 | | |
| **14a** | 0.35 | 0.71 | 0.94 | 12.5 | 15 | MIC | 27 |
| **14b** | 5 | 2.2 | 2.5 | 12.5 | 15 | μM | |
| **14c** | **7** | **15** | | **5** | | mm | 28 |
| **14d** | 5 | **14** | | **5** | | | |
| Stand | 6 | 12 | | 3 | | | |
| **15a** | **29** | | 14 | | | mm | 29 |
| **15b** | **30** | | 10 | | | | |
| $Cu(NO_3)_2$ | **32** | | 19 | | | | |
| Stand | 33 | | 29 | | | | |
| $HL^{16}$ | 10 | | 5 | | 2 | mm | 30 |
| **16a** | 14 | | 12 | | 4 | | |
| **16b** | 18 | | 18 | | 5 | | |
| Stand | 22 | | 20 | | 10 | | |
| **17** | **32** | | | **256** | | MIC | 31 |
| **18** | **16** | | | **256** | | μg/mL | |
| **19** | **16** | | | **128** | | | |
| Stand | 250 | | | >1024 | | | |
| $HL^{20}$ | 11 | | 9 | 10 | | mm | 32 |
| **20a** | 15 | | 16 | 11 | | | |
| **20b** | 18 | | 20 | 19 | | | |
| **20c** | 24 | | 23 | 21 | | | |
| **$HL^{21}$** | 8 | | 11 | 9 | | | |
| **21a** | 13 | | 11 | 17 | | | |
| **21b** | 17 | | 19 | 16 | | | |
| **21c** | 22 | | 21 | 20 | | | |
| Stand | 33 | | 31 | 31 | | | |

**Table 1.** (Contd.)

| Compound | Antimicrobial activity against *S. aureus* (*Sa*), *B. subtilis* (*Bs*), *E. coli* (*Ec*), *P. aeruginosa* (*Pa*), *C. albicans* (*Ca*) | | | | | | Reference |
|---|---|---|---|---|---|---|---|
| | *Sa* | *Bs* | *Ec* | *Pa* | *Ca* | units | |
| $H_2L$[22] | 14 | | | 13 | 15 | mm | 33 |
| **22a** | 18 | | | 15 | **20** | | |
| **22b** | 15 | | | 18 | **22** | | |
| **22c** | 14 | | | 17 | **23** | | |
| **22d** | N/a | | | 23 | 15 | | |
| Stand | 24 | | | 28 | 18 | | |
| HL[23] | | 18.3 | **22.6** | **18.3** | 16.9 | mm/mg sample | 34 |
| **23** | | 20.3 | **20.3** | N/a | 17.2 | | |
| HL[24] | | **32.4** | **19.9** | **17.3** | 19.6 | | |
| **24** | | **32.4** | **19.9** | **17.3** | **25.4** | | |
| HL[25] | | N/a | N/a | N/a | 11.2 | | |
| **25** | | **33.7** | 18.3 | 13.1 | 17.6 | | |
| HL[26] | | N/a | N/a | N/a | 13.3 | | |
| **26** | | 29.8 | 17.6 | 12.3 | 16.5 | | |
| HL[27] | | 19.2 | 13.6 | N/a | 15.9 | | |
| **27** | | 9.8 | 11.2 | N/a | 15.9 | | |
| Stand | | 32.4 | 19.9 | 17.3 | 25.4 | | |
| HL[28] | 12.1 | | 4.1 | | | $IC_{50}$ μmol/mL | 35 |
| **28** | **5.5** | | **5.8** | | | | |
| HL[29] | 1.9 | | 1.9 | | | | |
| **29** | **0.2** | | **0.2** | | | | |
| Stand | 5.8 | | 43.0 | | | | |
| **30** | 20 | | 21 | | 10 | mm | 36 |
| **31** | 18 | | 21 | | 10 | | |
| Stand | 21 | | 25 | | 19 | | |
| HL[32] | 64 | | 32 | | >512 | MIC μg/mL | 37 |
| **32a** | 1.0 | | **0.5** | | **16** | | |
| **32b** | 0.5 | | **0.25** | | **8** | | |
| Stand | 0.32 | | 2.12 | | >1024 | | |
| HL[33] | 128 | | >128 | | 16 | MIC μM | 38 |
| **33** | 16 | | 64 | | 32 | | |
| $H_2L$[34] | 85 | >100 | 18 | 67 | >100 | MIC μg/mL | 39 |
| **34a** | 22 | 14 | **0.5** | 28 | 0.7 | | |
| **34b** | 47 | 69 | 17 | 18 | 17 | | |
| **34c** | 26 | 18 | 16 | 11 | 16 | | |
| **34d** | 31 | 32 | 87 | 22 | 71 | | |
| Stand | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | | |

**Table 1.** (Contd.)

| Compound | Antimicrobial activity against *S. aureus* (*Sa*), *B. subtilis* (*Bs*), *E. coli* (*Ec*), *P. aeruginosa* (*Pa*), *C. albicans* (*Ca*) | | | | | | Reference |
|---|---|---|---|---|---|---|---|
| | *Sa* | *Bs* | *Ec* | *Pa* | *Ca* | units | |
| $L^{35}$ | N/a | | | | | MIC μg/mL | 40 |
| $Cu_2L^{35}$ | 395 | | | | | | |
| $Cu_2L^{35}/P_{60\%}$ | **0.64** | | | | | | |
| Stand | 2.4 | | | | | | |
| $HL^{36}$ | 37 | | 8 | | **39** | mm | 41 |
| **36a** | **40** | | 18 | | **40** | | |
| **36b** | **40** | | 16 | | **40** | | |
| $HL^{37}$ | 35 | | 15 | | **38** | | |
| **37a** | 20 | | 25 | | **40** | | |
| **37b** | 10 | | 10 | | **40** | | |
| Stand | 40 | | 35 | | 33 | | |
| $HL^{38}$ | 0.8 | 0.8 | 11 | 11 | 0.8 | mm | 42 |
| **38a** | **16** | 12 | 10 | **14** | 0.9 | | |
| **38b** | 10 | 06 | **16** | **11** | **18** | | |
| **38c** | **16** | 12 | 10 | **14** | 0.9 | | |
| **38d** | 12 | 0.7 | **17** | **10** | **17** | | |
| **38e** | 0.6 | 11 | 0.9 | **14** | 0.9 | | |
| Stand | 12 | 13 | 14 | 10 | 11 | | |
| $HL^{39}$ | N/a | | 10 | | | mm | 43 |
| $HL^{40}$ | 20 | | 19 | | | | |
| $HL^{41}$ | N/a | | 12 | | | | |
| $HL^{42}$ | 12 | | 15 | | | | |
| $HL^{43}$ | 19 | | **21** | | | | |
| $HL^{44}$ | **25** | | **21** | | | | |
| **39** | **32.5** | | **28** | | | | |
| **40** | **36** | | **31** | | | | |
| **41** | **32.5** | | **29** | | | | |
| **42** | **27** | | **26** | | | | |
| **43** | **38.5** | | **29.5** | | | | |
| **44** | **36.5** | | **30.5** | | | | |
| CF | 21 | | 21 | | | | |
| $HL^{45}$ | 7 | 8 | 2 | | 3 | mm | 57 |
| **45a** | 7 | 14 | 5 | | 8 | | |
| **45b** | 25 | 18 | 9 | | 11 | | |
| **45c** | 13 | 16 | 3 | | 13 | | |
| **45d** | 14 | 15 | 5 | | 17 | | |
| **45e** | 7 | 14 | 3 | | 8 | | |
| **45f** | 14 | 18 | 5 | | 5 | | |
| **45g** | 14 | 20 | 12 | | 14 | | |
| **45h** | 18 | 9 | 7 | | 11 | | |
| Stand | 35 | 35 | 27 | | 28 | | |

**Table 1.** (Contd.)

| Compound | Antimicrobial activity against *S. aureus* (*Sa*), *B. subtilis* (*Bs*), *E. coli* (*Ec*), *P. aeruginosa* (*Pa*), *C. albicans* (*Ca*) | | | | | | Reference |
|---|---|---|---|---|---|---|---|
| | *Sa* | *Bs* | *Ec* | *Pa* | *Ca* | units | |
| HL[46] | >256 | | >256 | >256 | | MIC μM | 58 |
| HL[47] | >256 | | 256 | >256 | | | |
| HL[48] | 128 | | 128 | 256 | | | |
| **46** | 128 | | 128 | 128 | | | |
| **47** | 32 | | 16 | 16 | | | |
| **48** | 16 | | 8 | 8 | | | |

* Values exceeding the activity of standard antibiotics are highlighted.
** Standard antibiotic used for comparison.
*** Not active.
**** Iinhibition zone diameter.

antibiotic used for comparison. The leading position is occupied by copper complexes with N,O-donor ligands (for example, compounds **17**–**19**, **22a**–**22d**, **23**–**25**, **28**–**32**). Therefore, researchers are advised to pay attention to this group of copper complexes.

In most studies, a higher antimicrobial activity of metal complexes is noted compared to free ligands [11, 14, 16, 20–22, 24, 25, 30, 32, 33, 35, 37–39, 41, 57, 58]. To explain this fact, the authors [11, 22, 36, 38] appeal to Tweedy's chelation theory [12], quoting the following explanation "The high activities of the complexes can be explained by the cell permeability concept and/or Tweedy's chelation theory. According to the cell permeability concept, the metal ions can hardly pass through the membrane surrounding the cell due to the high polarity of such ions. On chelation, the polarity of the Cu(II) ions can be reduced to a greater extent as a result of the overlap of the ligand and metal ion orbitals leading to a partial sharing of the positive charge of the metal ion with donor groups. Furthermore, the lipophilicity of complexes is improved as the *p*-electron delocalization over the whole chelating ring increases. Subsequently, the penetration of the complexes into lipid membranes will be enhanced and then blocking the Cu(II) binding sites in the enzymes of microorganisms." It is quite logical reasoning, which is appropriate if we take into account the comparison of the activity of a copper salt and its complex compound, as was done [22]. The authors [38] add that "the enhancement of the activity can occur not only due the increase of lipophilicity but alternatively it may be due to the formation of reactive oxygen species (ROS) through the reduction of Cu(II) to Cu(I) in intracellular environment, which can cause the death of the microorganism."

Comparison of copper complexes with other metal complexes generally indicates that copper compounds are more effective antibacterial and/or antifungal agents [11, 14, 25, 30, 32, 33, 39, 41, 42, 56]. This can be associated with such a distinctive feature of copper as its ability to redox transformations.

In order to study the mechanism of antimicrobial action of drugs in a number of works, the interaction of copper complexes with deoxyribonucleic acid (DNA) fragments was studied using methods such as electron spectroscopy, viscometry [11, 13, 14, 28, 29, 32, 39, 56]. In most studies, a correlation has been established between the high antimicrobial activity of metal complexes and the efficiency of their interaction with DNA fragments.

Unfortunately, the studies of the biological activity of metal complexes in the studies analyzed are not systematic. Most often it is as a small supplement to the synthetic and structural-chemical part of the study. The fact that very promising antimicrobial agents have been identified in certain groups of copper complexes makes it possible to recommend combining the efforts of chemists and biologists for more extensive targeted research in this direction.

## FUNDING

This work has been supported by Russian Foundation for Basic Research (RFBR) (project no. 20-03-00027).

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## REFERENCES

1. Frei, A., Zuegg, J., Elliott, A.G., et al., *Chem. Sci.*, 2020, vol. 11, p. 2627. https://doi.org/10.1039/C9SC06460E
2. Sovari, S.N. and Zobi, F., *Chemistry*, 2020, vol. 2, p. 418. https://doi.org/10.3390/chemistry2020026

3. Morrison, C.N., Prosser, K.E., Stokes, R.W., et al., *Chem. Sci.*, 2020, vol. 11, p. 1216. https://doi.org/10.1039/c9sc05586j
4. Franz, K.J. and Metzler-Nolte, N., *Chem. Rev.*, 2019, vol. 119, p. 727. https://doi.org/10.1021/acs.chemrev.8b00685
5. Loginova, N.V., Harbatsevich, H.I., Osipovich, N.P., et al., *Curr. Med. Chem.*, 2020, vol. 27, p. 5213. https://doi.org/10.2174/0929867326666190417143533
6. Duncan, C. and White, A.R., *Metallomics*, 2012, vol. 4, no. 2, p. 127. https://doi.org/10.1039/c2mt00174h
7. Santini, C., Pellei, M., Gandin, V., et al., *Chem. Rev.*, 2014, vol. 114, p. 815. https://doi.org/10.1021/cr400135x
8. Williams, D.R., *The Metals of Life: The Solution Chemistry of Metal Ions in Biological Systems*, London: Van Nostrand-Reinhold, 1971.
9. Hordyjewska, A., Popiołek, L., and Kocot, J., *Biometals*, 2014, vol. 27, p. 611. https://doi.org/10.1007/s10534-014-9736-5
10. Balsano, C., Porcu, C., and Sideri, S., *Metallomics*, 2018, vol. 10, p. 1712. https://doi.org/10.1039/c8mt00219c
11. Sakthivel, A., Thangagiri, B., Raman, N., et al., *J. Biomol. Struct. Dyn.*, 2020. https://doi.org/10.1080/07391102.2020.1801508
12. Tweedy, B.G., *Phytopatology*, 1964, vol. 55, p. 910.
13. Gungor, O., Kocer, F., and Kose, M., *J. Mol. Struct.*, 2020, vol. 1204, article 127533. https://doi.org/10.1016/j.molstruc.2019.127533
14. Kalarani, R., Sankarganesh, M., Kumar, G.G.V., and Kalanithi, M., *J. Mol. Struct.*, 2020, vol. 1206, article 127725. https://doi.org/10.1016/j.molstruc.2020.127725
15. Batool, S.S., Gilani, S.R., Zainab, S.S., et al., *Polyhedron*, 2020, vol. 17, article 114346. https://doi.org/10.1016/j.poly.2020.114346
16. Batool, S.S., Gilani, S.R., Zainab, S.S., et al., *J. Coord. Chem.*, 2020, vol. 73, p. 1778. https://doi.org/10.1080/00958972.2020.1795147
17. Batool, S.S., Gilani, S.R., Tahir, M.N., and Ruffer, T., *J. Mol. Struct.*, 2017, vol. 1148, p. 714. https://doi.org/10.1016/j.molstruc.2017.07.014
18. Batool, S.S., Gilani, S.R., Tahir, M.N., et al., *J. Coord. Chem.*, 2018, vol. 71, p. 2569. https://doi.org/10.1080/00958972.2018.1503653
19. Batool, S.S., Gilani, S.R., Zainab, S.S., et al., *J. Struct. Chem.*, 2019, vol. 60, p. 1156. https://doi.org/10.1134/s0022476619070187
20. Aycan, T., Ozturk, F., Doruk, T., et al., *Spectrochim. Acta, A*, 2020, vol. 241, article 118639. https://doi.org/10.1016/j.saa.2020.118639
21. Srivastava, A.K., Singh, S.K., and Srivastava, A., *Chem. Data Collections*, 2020, vol. 26, article100357. https://doi.org/10.1016/j.cdc.2020.100357
22. Dimitrijević, T., Novaković, I., Radanović, D., et al., *J. Coord. Chem.*, 2020, vol. 73, p. 702. https://doi.org/10.1080/00958972.2020.1740212
23. Gordon, A.T., Abosede, O.O., and Ntsimango, S., *Inorg. Chim. Acta*, 2020, vol. 510, article119744. https://doi.org/10.1016/j.ica.2020.119744
24. Obaleye, J.A., Ajibola, A.A., Bernardus, V.B., et al., *Inorg. Chim. Acta*, vol. 503, article 119404. https://doi.org/10.1016/j.ica.2019.119404
25. Balan, G., Burduniuc, O., Usataia, I., et al., *Appl. Organomet. Chem.*, 2020, vol. 34, article e5423. https://doi.org/10.1002/aoc.5423
26. Soliman, S.M., El-Faham, A., and El Silk, S.E., *Appl. Organomet. Chem.*, 2020, vol. 34, article e5941. https://doi.org/10.1002/aoc.5941
27. Wojciechowska, A., Szuster-Ciesielska, A., Sztandera, M., et al., *Appl. Organomet. Chem.*, 2020, vol. 34, article e5698. https://doi.org/10.1002/aoc.5698
28. Dhakshanamoorthy, S., Krishnan, M.M., and Arumugham, M.N., *J. Chem. Bio. Phys. Sci., A*, 2020, vol. 10, p. 107. https://doi.org/10.24214/jcbps.a.10.2.10718
29. Saravanan, P.C., Ezhilarasan, D., and Arumugham, M.N., *J. Chem. Bio. Phys. Sci., A*, 2020, vol. 10, p. 33. https://doi.org/10.24214/jcbps.a.10.1.03344
30. Kumari, S.S., *Asian J. Chem.*, 2020, vol. 32, p. 192. https://doi.org/10.14233/ajchem.2020.21801
31. Zhu, H.-Y., *Inorg. Nano-Met. Chem.*, 2020. https://doi.org/10.1080/24701556.2020.1813175
32. Ramesh, G., Daravath, S., Ganji, N., et al., *J. Mol. Struct.*, 2020, vol. 1202, article 127338. https://doi.org/10.1016/j.molstruc.2019.127338
33. El-Razek, S.E.A., El-Gamasy, S.M., Hassan, M., et al., *J. Mol. Struct.*, 2020, vol. 1203, article 127381. https://doi.org/10.1016/j.molstruc.2019.127381
34. El-Dissouky, A., Abu-Elsoud, E.S., Abdel Razik, A., et al., *Appl. Organomet. Chem.*, 2020, vol. 34, article e5953. https://doi.org/10.1002/aoc.5953
35. Ayaz, F., Gonul, L., Demirbag, B., and Ocakoglu, K., *Appl. Biochem. Biotechnol.*, 2020, vol. 191, p. 716. https://doi.org/10.1007/s12010-019-03223-7
36. El-Medani, S.M., Makhlouf, A.A., Moustafa, H., et al., *J. Mol. Struct.*, 2020, vol. 1208, article 127860. https://doi.org/10.1016/j.molstruc.2020.127860
37. Xue, L.-W., Zhang, H.-J., and Wang, P.-P., *Inorg. Nano-Met. Chem.*, 2020, vol. 50, p. 637. https://doi.org/10.1080/24701556.2020.1723627
38. Santiago, P.H.O., Tiago, F.S., Castro, M.S., et al., *J. Inorg. Biochem.*, 2020, vol. 204, article 110949. https://doi.org/10.1016/j.jinorgbio.2019.110949
39. Shiju, C., Arish, D., and Kumaresan, S., *J. Mol. Struct.*, 2020, vol. 1221, p. 128770. https://doi.org/10.1016/j.molstruc.2020.128770
40. Sharma, B., Clem, C.M., Diaz Perez, A., and Striegler, S., *ACS Appl. Bio Mater.*, 2020, vol. 3, p. 7611. https://doi.org/10.1021/acsabm.0c00820
41. Abdi, Y., Bensouilah, N., Siziani, D., et al., *J. Mol. Struct.*, 2020, vol. 1202, article 127307. https://doi.org/10.1016/j.molstruc.2019.127307
42. Patel, H.P., *Int. J. Curr. Res.*, 2020, vol. 12, p. 9173. https://doi.org/10.24941/ijcr.37598.01.2020

43. Khalil, T.E., El-Dissouky, A., Al-Wahaib, D., et al., *Appl. Organomet. Chem.*, 2020, vol. 34, article e5998. https://doi.org/10.1002/aoc.5998

44. Kaushal, M., Lobana, T.S., Nim, L., Bala, R., Arora, D.S., Garcia-Santos, I., Duff, C.E., and Jasinski, J.P., *New J. Chem.*, 2019, vol. 43, p. 11727. https://doi.org/10.1039/c9nj01459d

45. Oladipo, S.D., Omondi, B., and Mocktar, C., *Polyhedron*, 2019, vol. 170, p. 712. https://doi.org/10.1016/j.poly.2019.06.038

46. Binzet, G., Gumus, I., Dogen, A., et al., *J. Mol. Struct.*, 2018, vol. 1161, p. 519. https://doi.org/10.1016/j.molstruc.2018.02.073

47. Gulea, A.P., Graur, V.O., Chumakov, Yu.M., et al., *Russ. J. Gen. Chem.*, 2019, vol. 89, p. 953. https://doi.org/10.1134/S1070363219050153

48. Ibrahim, A.B.M., Farh, M.K., and Mayer, P., *Inorg. Chem. Commun.*, 2018, vol. 94, p. 127. https://doi.org/10.1016/j.inoche.2018.06.019

49. Jawoor, S.S., Patil, S.A., and Toragalmath, S.S., *J. Coord. Chem.*, 2017, vol. 71, p. 271. https://doi.org/10.1080/00958972.2017.1421951

50. Katugampala, S., Perera, L.C., Nanayakkara, C., and Perera, T., *Bioinorg. Chem. Appl.*, 2018, vol. 2018, article 2530851. https://doi.org/10.1155/2018/2530851

51. Onwudiwe, D.C. and Ekennia, A.C., *Res. Chem. Intermed.*, 2016, vol. 43, p. 1465. https://doi.org/10.1007/s11164-016-2709-2

52. Anacona, J.R., Mago, K., and Camus, J., *Appl. Organomet. Chem.*, 2018, vol. 32, article e4374. https://doi.org/10.1002/aoc.4374

53. El-Gammal, O.A., El-Reash, G.M.A., and Bedier, R.A., *Appl. Organomet. Chem.*, 2019, vol. 33, article e5141. https://doi.org/10.1002/aoc.5141

54. Öztürk, F., Aycan, T., and Özdemir, N., *J. Coord. Chem.*, 2019, vol. 72, p. 3359. https://doi.org/10.1080/00958972.2019.1692201

55. Oliveira, A.A., Oliveira, A.P.A., Franco, L.L., et al., *Biometals*, 2018, vol. 31, p. 571. https://doi.org/10.1007/s10534-018-0106-6

56. Ali Khan, U., Badshah, A., Nawaz Tahir, M., and Khan, E., *Polyhedron*, 2020, vol. 181, article 114485. https://doi.org/10.1016/j.poly.2020.114485

57. Adly, O.M.L., Taha, A., Ibrahim, M.A., and Fahmy, S.A., *Appl. Organomet. Chem.*, 2020, vol. 34. p. e5763. https://doi.org/10.1002/aoc.5763

58. Qi, J., Wang, X., Liu, T., et al., *J. Coord. Chem.*, 2020, vol. 73, p. 1208. https://doi.org/10.1080/00958972.2020.1768378

59. Kargar, H., Ardakani, A.A., Tahir, M.N., et al., *J. Mol. Struct.*, 2021, vol. 1229, article 129842. https://doi.org/10.1016/j.molstruc.2020.129842

60. Azam, M., Mohammad, S.W., Alam, M., et al., *Polyhedron*, 2021, vol. 195, article 114991. https://doi.org/10.1016/j.poly.2020.114991

61. Ismael, M., Abdel-Mawgoud, M., Rabia, M.K., and Abdou, A., *J. Mol. Struct.*, 2021, vol. 1227, article 129695. https://doi.org/10.1016/j.molstruc.2020.129695

62. Bosch, P., Staneva, D., Vasileva-Tonkova, E., et al., *Materials*, 2020, vol. 13, p. 4574. https://doi.org/10.3390/ma13204574

63. Shchegolkov, E.V., Shchur, I.V., Burgart, Y.V., et al., *Polyhedron*, 2021, vol. 194, article 114900. https://doi.org/10.1016/j.poly.2020.114900

64. U-wang, O., Singh, R.K.B., Singh, U.I., et al., *Asian J. Chem.*, 2020, vol. 32, p. 2783. https://doi.org/10.14233/ajchem.2020.22827

65. Meena, A., Sharma, R., and Sukhadia, V., *Curr. Phys. Chem.*, 2020, vol. 10, p. 213. https://doi.org/10.2174/1877946810666200116091321

66. Sukhadia, V., Sharma, R., and Meena, A., *Curr. Phys. Chem.*, 2020, vol. 10, p. 229. https://doi.org/10.2174/1877946810666200221122053

67. Aiyelabola, T.O., Akinkunmi, E.O., and Akinade, R., *Adv. Biolog. Chem.*, 2020, vol. 10, p. 25. https://doi.org/10.4236/abc.2020.102003

68. Alterhoni, E., Tavman, A., Hacioglu, M., et al., *J. Mol. Struct.*, 2020, vol. 1229, article 129498. https://doi.org/10.1016/j.molstruc.2020.129498

69. Touj, N., Al Nasr, I.S., and Koko, W.S., *J. Coord. Chem.*, 2020, vol. 73, p. 2889. https://doi.org/10.1080/00958972.2020.1836359