Chapter 4

Transition Metal Complexes with Antipyrine-Derived Schiff Bases: Synthesis and Antibacterial Activity

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Additional information is available at the end of the chapter

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Abstract

The increase of death rate, associated with infectious diseases, is directly linked to the bacteria that have multiple resistance to antibiotics. The lack of efficient medical treatment is the main cause of this problem. The synthesis of new antibacterial agents, through various methods, is, for sure, an emergency medical issue. Recent research focuses more and more on the synthesis of complexes of the transitional metals with ligands of Schiff-base type, as a result of the biological properties which they have. This article presents the synthesis of several complexes with base Schiff ligands, derived from 4-aminoantipyrine and in vitro research of their antibacterial activities. The new compounds were tested for their in vitro antibacterial activity against *Staphylococcus aureus var. Oxford 6538, Klebsiella pneumoniae ATCC* 100131, *Escherichia coli ATCC 10536*, and *Pseudomonas aeruginosa ATCC 9027* strains. Based on the "*in vitro*" studies, we can say that ten of the complexes synthetized can be successfully used instead of streptomycin, where there is resistance to this antibiotic.

Keywords: 4-aminoantipyrine, Schiff bases, metal complexes, antibacterial agents, streptomycin

1. Introduction

The synthesis of new antibacterial agents, through various methods, is, for sure, an emergency medical issue [1–3]. Schiff bases are important precursors for the synthesis of some bioactive compounds [4, 5]. Schiff bases have received considerable attention since the discovery of their antibacterial [6, 7], antifungal [8], anti-HIV [9, 10], anti-inflammatory [11], anticonvulsant [12, 13], antiviral [14], and anticancer properties [15–17]. The presence of the inimical grouping in these organic ligands plays an important part in manifesting these biological characteristics

[18–20]. Schiff bases can be regarded as promising antimicrobial agents. For example, N-(salicylidene)-2-hydroxyaniline proved efficiency against *Mycobacterium tuberculosis* H37Rv, exhibiting an MIC value of 8 μg/mL [21]. The 5-chloro-salicylaldehyde-Shiff base derivatives are efficient against *Pseudomonas fluorescence* (MIC=2.5–5.2 μg/mL), *Escherichia coli* (MIC=1.6–5.7 μg/mL), *Bacillus subtilis* (MIC=1.8 μg/mL), and *Staphylococcus aureus* (MIC=1.6 and 3.1 μg/mL), respectively, while the MIC values for the reference drug kanamycin against the same bacterial strains were 3.9 μg/mL [22]. Some of the isatin-derived Schiff bases have shown antibacterial activity against *Escherichia coli* NCTC 10418 (MIC=2.4 μg/mL), *Vibrio cholerae* non-01(MIC=0.3 μg/mL), *Enterococcus faecalis* (MIC=1.2 μg/mL), and *Proteus shigelloides* (MIC=4.9 μg/mL). The MIC values for the reference drug sulfamethoxazole against the same bacterial strain were in the range of 312–5000 μg/mL. Therefore, these compounds were proven to be 1040-, 1040-, 4160-, and 1020-fold more potent than sulfamethoxazole [23, 24]. The studies run on the Schiff bases, derived from the isoniazid have allowed to identify a compound which has turned out to have a therapeutical effectiveness and safety, that is, 4000 times higher than that of isoniazid [25].

The morpholine-derived Schiff bases was effective against *Staphylococcus aureus* (MIC=20 μg/mL), *Micrococcus luteus* (MIC=32 μg/mL), *Streptococcus epidermidis* (MIC=17 μg/mL), *Bacillus cereus* (MIC=21 μg/mL), and *Escherichia coli* (MIC=16 μg/mL).

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety completely inhibited the growth of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. MIC values for these compounds varied from 6.3 to 12.5 μg /mL, which are comparable to those obtained for the reference drug ciprofloxacin [26]. Lately, within the last couple of years, a special attention has been paid to the chemistry of the metal complexes of the Schiff bases. This is due to the chemical stability of the complexes as well as to the possibility of using them in the most varied fields. To a great extent, remarkable successes, in this field, have been obtained due to the various synthesis methods of the complexes. Recent research focuses more and more on the synthesis of complexes of the transitional metals with ligands of Schiff-base type, as a result of the biological properties which they have. In many cases, the conclusion has been that, through the coordination of the Schiff bases, to the metal ions, which are present in the biological systems, the biological activity of the respective Schiff base increases. A large number of Schiff bases and the corresponding metal complexes have proven antibacterian, antifungal, antitumor, and antileukemia activity [27–29].

Ever since it was synthesized [30], antipyrine (1-fenil-2,3-dimetil-5-pirazolona) has enjoyed a lot of attention due to its analgesic and antipyretic properties. The discovery of these properties has allowed for deeper research on antipyrine and its derivatives. Thus, 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (4-aminoantipyrine) was discovered, a derivative with analgesic action, antipyretic, anti-inflammatory, antibacterian, and antineoplastic [31, 32]. The derivatives of 4-aminoantipyrine are used in the synthesis of azo-colorant, in analytical chemistry for spectrophotometric determination of metal ions [33], in pharmacology, as an effective antitumor [34], analgesic [35], antiviral [36], anti-inflammatory [37], anticancer [38], and antimicrobial drugs [39–42].

Lately, the research has been conducted in order to get metal complexes with a wide range of biological activities and with the lowest level of toxicity. In this work, the synthesis of some complexes with base Schiff ligands is presented, derived from 4-aminoantipyrine and in vitro research of their antibacterial activities.

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2. Experimental

2.1. Metal complexes with aminoantipyrine Schiff bases: structure and methods of synthesis

Complexes of Cu(II), Co(II), Ni(II), Zn(II), Mn(II), VO(II), and Fe(III) were prepared by direct reaction between Schiff base ligand and the corresponding metal salts.

The next Schiff bases were synthesized:

- 1-phenyl-2,3-dimethyl-4-(N- acetoacetanilide)-3-pyrazolin-5-one (**HL**[1])
- 1,5-dimethyl-2-phenyl-4-(1-(pyridin-2-yl)ethylideneamino)-1H-pyrazol-3(2H)-one (**HL**[2])
- 5-nitro-salicylidene-4-aminoantipyrine (**HL**[3]**)**
- 4-((E)-4-((E)-(4-chlorophenyl)diazenyl)-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (**HL**[4])
- 1-phenyl-2,3-dimethyl-4-(N-imidazole-2-carboxaldehyd)-3-pyrazolin-5-one (**HL**[5])
- 4-(2-pyrrolylmethylideneamino)antipyrine (**HL**[6])
- 4[(benzylidene)amino]antipyrine (**HL**[7])
- 4[(cinnamalidene)amino]antipyrine (**HL**[8])
- 4[(2-chlorobenzylidene)amino]antipyrine (**HL**[9])
- 4-[(furan-2-ylmethylene)amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3Hpyrazol-3-one(**HL**[10])
- 1-phenyl-2,3–dimethyl-4-(2-hydroxy-5-nitro-benzylideneamino)-3-pyrazolin-5-one (**HL**[11])
- salicylidene-4-aminoantipyrine (**HL**[12])
- salicylidene-4-aminoantipyrinyl-2-amino-3-hydroxypyridine (**HL**[13])
- napthylidene-4-aminoantipyrine (**HL**[14])
- 5-[(E)-[(3Z)-3-[2-[(Z)-[4-[(E)-(3-hydroxy-4-nitro-phenyl)methyleneamino]-1,5-dimethyl-2-phenyl-pyrazol-3-ylidene]amino]phenyl]imino-1,5-dimethyl-2-phenyl-pyrazol-4-yl] iminomethyl]-2-nitro-phenol (**HL**[15])
- 4-[(E)-[(3Z)-3-[2-[(Z)-[4-[(E)-(4-hydroxy-3-methoxy-phenyl)methyleneamino]-1,5-dimethyl-2-phenyl-pyrazol-3-ylidene]amino]phenyl]imino-1,5-dimethyl-2-phenyl-pyrazol-4-yl]iminomethyl]-2-methoxy-phenol (**HL**[16])
- 3-salicylideneacetylacetone-2,4-di(imino-4′-antipyrinyl)pentane (**HL**[17])
- 2,6-diformyl-4-methylphenol bis(4-amino-3-antipyrine) (**HL**[18]**)**
- 4,4′-(1E,1′E)-(1,1′-(pyridine-2,6-diyl)bis(ethan-1-yl-1-ylidene))bis(azan-1-yl-1-ylidene) bis (1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one) (**HL**[19]**)**
- 3(3′-hydroxy-4′-nitrobenzalidene)-2,4-di(imino-4′-antipyrinyl)pentane (**HL**[20])

2.1.1. Synthesis of the complexes with HL^{1-5} *ligands*

The metal complexes with these Schiff bases are obtained by adding a methanolic or ethanolic ligand solution to a solution of metal salt, in a molar ratio L:M=2:1 [43, 44] or 1:1 [45–47]. The mixture of reaction is refluxed for 2–5h or stirring for 12h. The precipitate is obtained that is filtered, washed with ether, methanol or ethanol, and dried *in vacuo* (**Figures 1–4**).

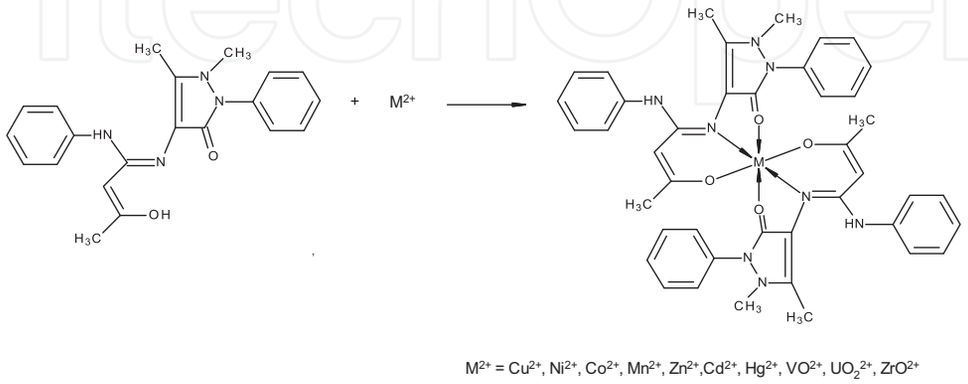

Figure 1. Scheme of synthesis of complexes with ligand HL^{1}.

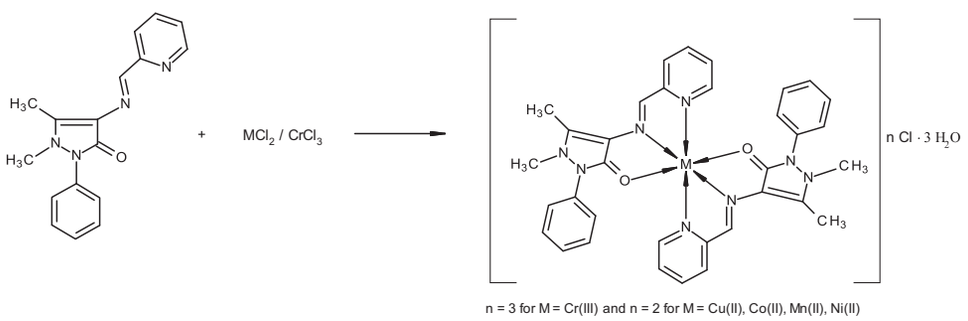

Figure 2. Scheme of synthesis of complexes with ligand HL^{2}.

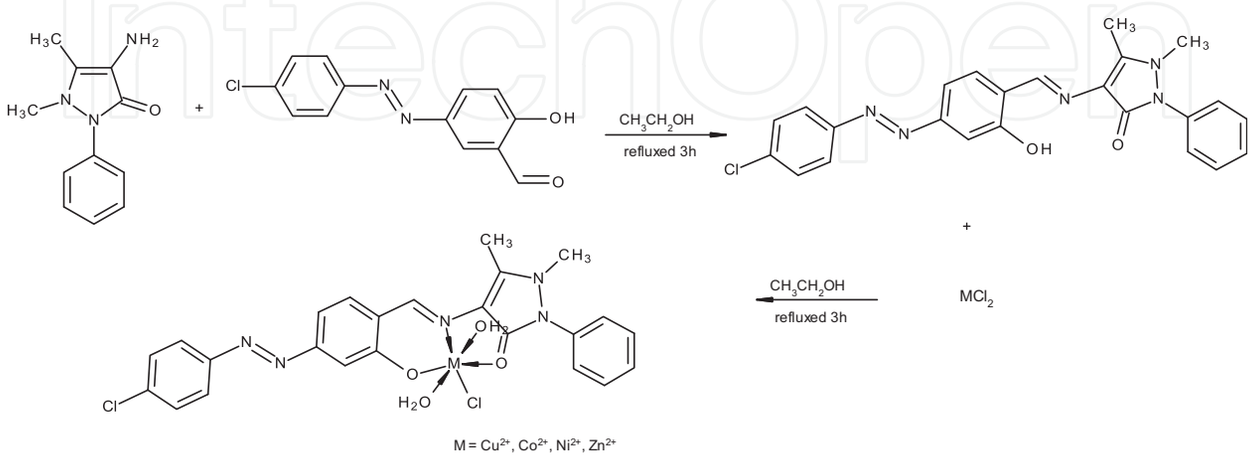

Figure 3. Scheme of synthesis of complexes with ligand HL^{4}.

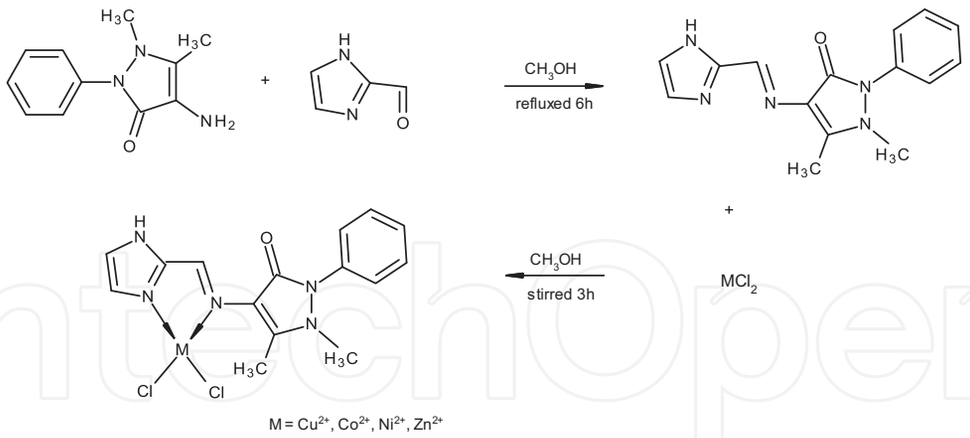

Figure 4. Scheme of synthesis of complexes with ligand **HL**[5].

2.1.2. Synthesis of the complexes with ligands ***HL*** [6–11] *and various co-ligands*

The metal complexes with ligands base Schiff ***HL*** [6–11] are obtained through three methods:

Method 1. Previously, the complex combination with the Schiff base is obtained to which the co-ligand is added(α-picoline, β-picoline, γ-picoline, n-propylamine). After the complete precipitation, the solid compound is obtained that is filtered, washed with ether, and dried in the exicator (**Figure 5**) [48].

Method 2. The mixture of reaction which contains the alcoholic ligand solutions (the Schiff base and the co-ligand) and the alcoholic solution of metal salt is refluxed for 6–8h. After the concentration of the solution to a third of its volume, on the water bath, a precipitate is obtained which is filtered, washed with alcohol, and dried in vacuo (**Figure 6**) [49]; (**Figure 7**) [50, 51].

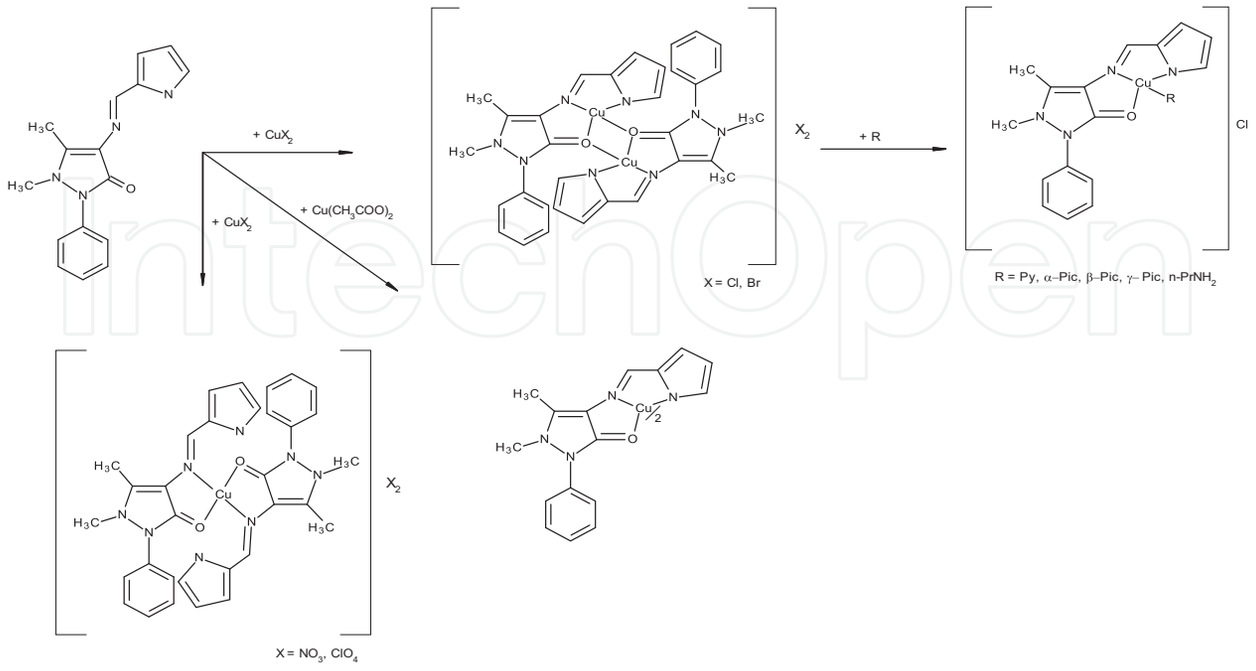

Figure 5. Scheme of synthesis of complexes with ligand **HL**[6].

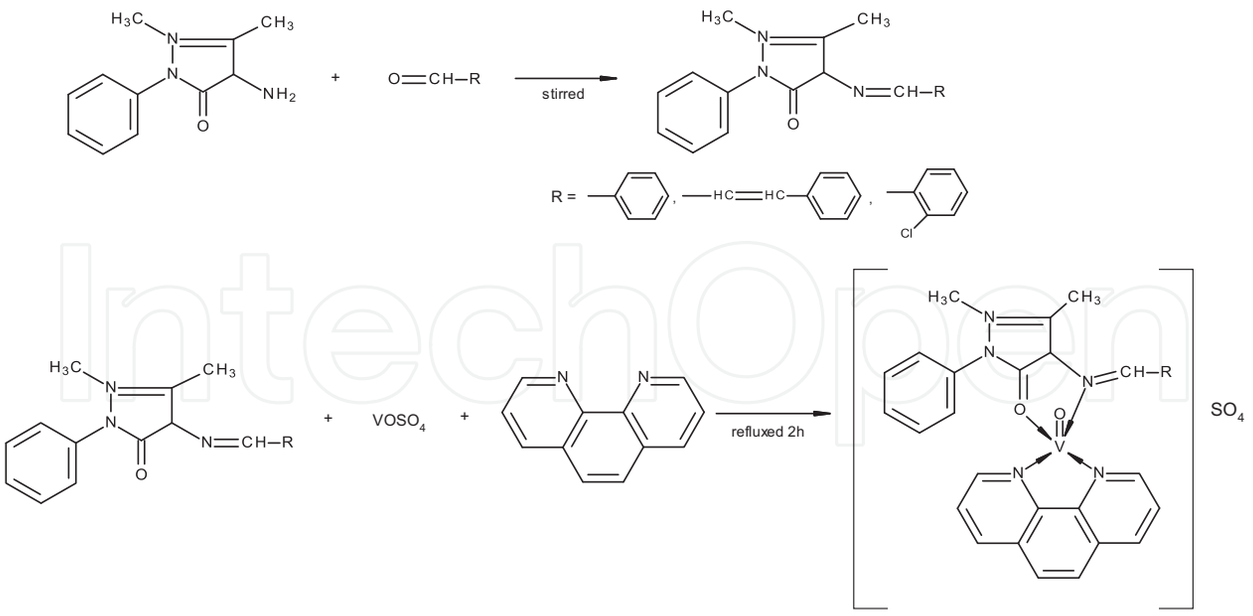

Figure 6. Scheme of synthesis of complexes with ligands **HL**[7–9].

Method 3. By adding an ethanolic solution of Schiff base to a metal salt solution, in a molar ratio 1:1, a mixture is obtained which is refluxed for 3–8h. An ethanol solution of co-ligand (amino acids; 1,10-phenanthroline; 2,2′- bipyridine; etc.) is added in the reaction environment, and the reflux is kept going on for another 1–3h. The precipitate is obtained which is filtered, washed in ether, and dried in vacuo (**Figure 7**) [52, 53]; (**Figure 8**) [54].

2.1.3. Synthesis of the complexes with ligands ***HL***[10, 12–14] *and various aromatic amine*

The metal complexes with these Schiff bases are obtained through refluxing, lasting for 3–4h of a mixture that contains the metal salt dissolved in ethanol and the ligand dissolved in the same solvent. The ligand can be previously obtained through two different methods (**Figure 9**) [55], respectively (**Figure 10**) [53, 56–58].

2.1.4. Synthesis of the complexes with ligands ***HL***[15] *and* ***HL***[16]

The metal complexes with ligands Schiff bases **HL**[15] and **HL**[16] are obtained by treating a ligand solution with a solution of metal salt, in a molar ratio L:M=1:1. The mixture is refluxed for 5–6h. After the concentration of the solution to a third of its volume, on the water bath, a precipitate is obtained which is filtered, washed with ether, and dried in vacuo (**Figure 11**) [59, 60].

2.1.5. Synthesis of the complexes with ligands ***HL***[17–20]

The metal complexes with Schiff base ligands **HL**[17–20] are obtained through treating a solution that contains the ligand dissolved in ethanol or acetonitrile with the solution of metal salt, in a molar ratio of L:M=1:1. The mixture is refluxed for 5–6h (**Figures 12**, **13**) [61–64] or, in other cases, even 12h (**Figure 14**) [45]. The precipitation begins immediately or after the concentration of the solution to a third of its volume, on a water bath. The precipitate is obtained which is filtered, washed with ether, and dried in vacuo.

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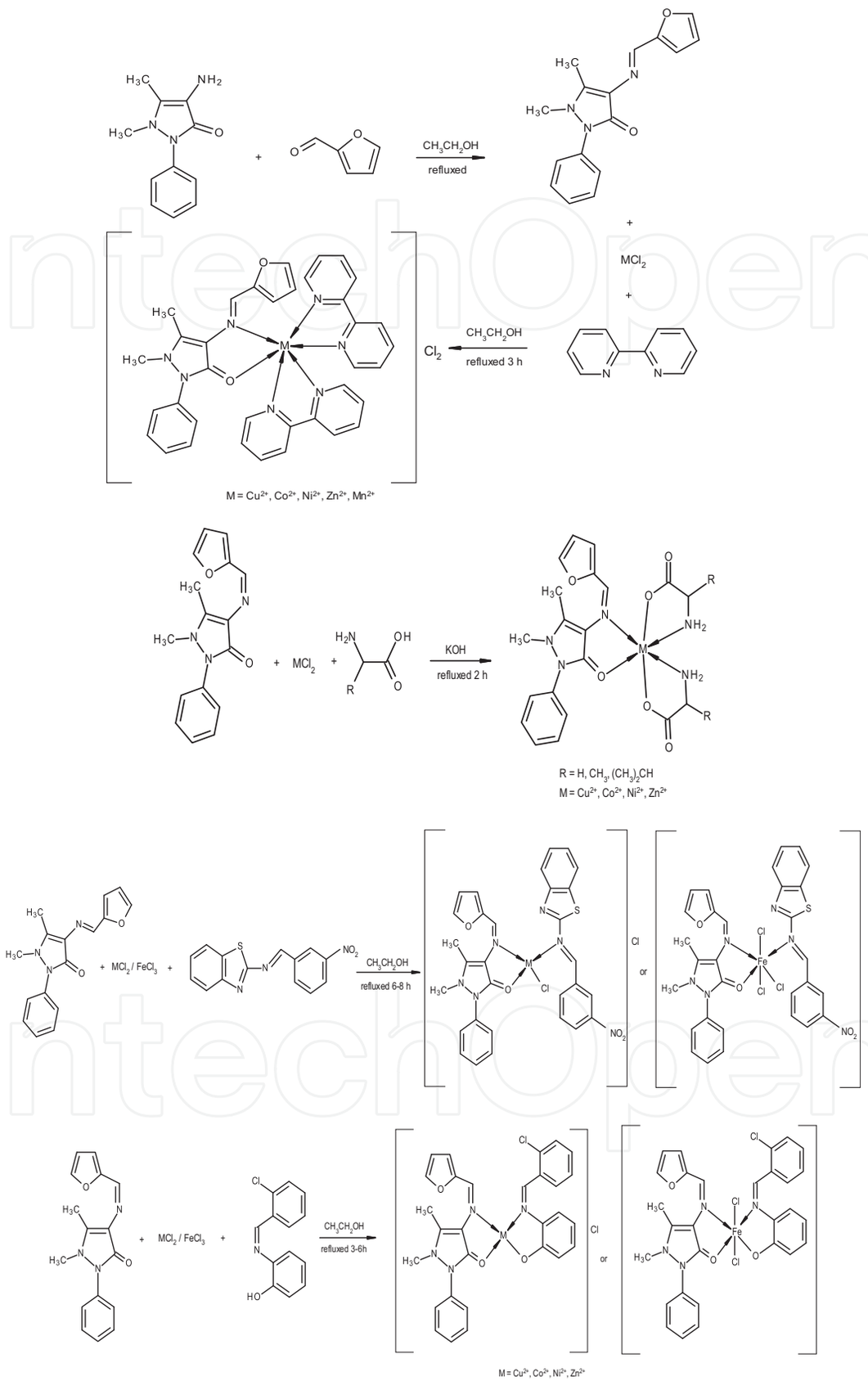

Figure 7. Scheme of synthesis of complexes with ligand **HL[10]**.

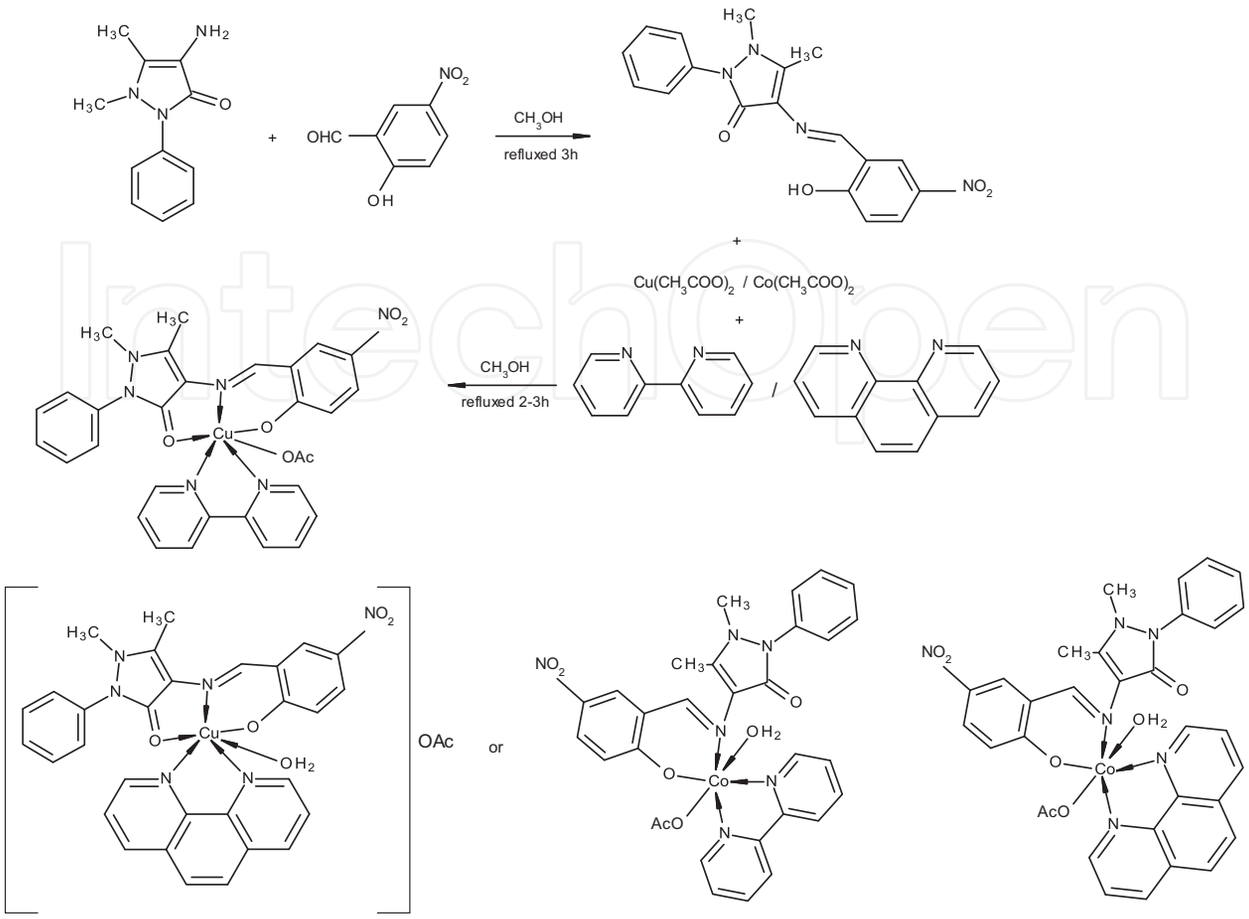

Figure 8. Scheme of synthesis of complexes with ligand **HL**[11].

The study methods used to describe the complexes were as follows: the basic chemical analysis, spectrometry IR, UV-VIS, EPR, the thermogravimetric analysis, the magnetic susceptibility, and the molar electric conductibility. The complexes synthetized were tested from the point of view of the antibacterian activity; the obtained results were presented in the respective papers.

2.2. New compounds: structure and antibacterial activity

2.2.1. Structure and synthesis of the compounds 1–28

With a view to obtaining new compounds with significant antibacterian activity, we have synthesized and characterized a series of complexes of Cu(II), Ni(II), Mn(II), and V(IV) with ligands Schiff bases, derived from 4-aminoantipyrine.

In this regard, we have synthesized four ligands, with chromophore groups ONO, respectively, ON, and different volumes of the aldehyde which is a part of Schiff base: 1-phenyl-2,3-dimethyl-4-(N-3-formyl-6-methyl-chromone)-3-pyrazolin-5-one (**HL**[21]); 1-phenyl-2,3-dimethyl-4-(N-2-hydroxy-4-methoxy-benzaldehyde)-3-pyrazolin-5-one (**HL**[22]); 1-phenyl-2,3-dimethyl-4-(1H-indole-3-carboxaldehyde)-3-pyrazolin-5-one (**HL**[23]); 1-phenyl-2,3-dimethyl-4-(N-pyridoxal hydrochloride)-3-pyrazolin-5-one (**HL**[24]) as well as their complex combinations with transitional metals: Cu^{2+}, Ni^{2+}, Mn^{2+}, VO^{2+} (28 metal complexes).

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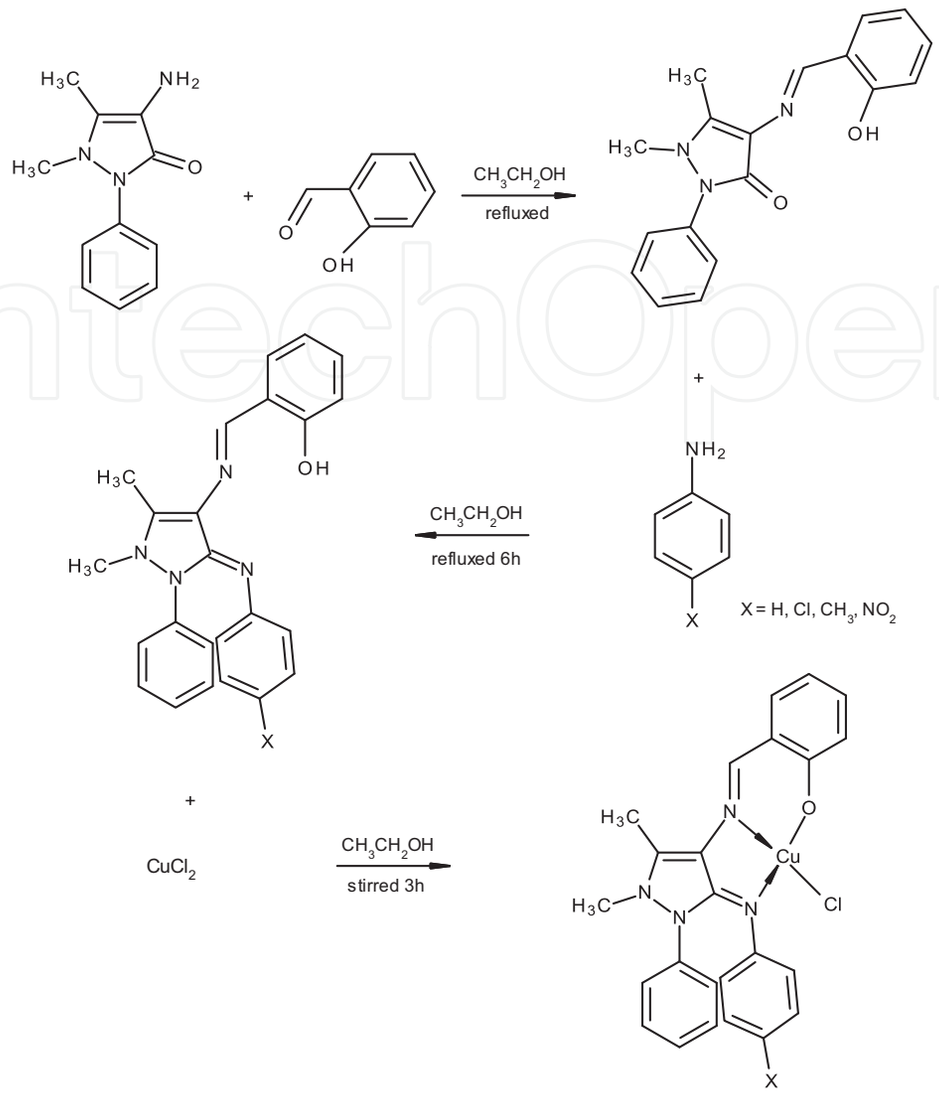

Figure 9. Scheme of synthesis of complexes with ligand **HL**[12].

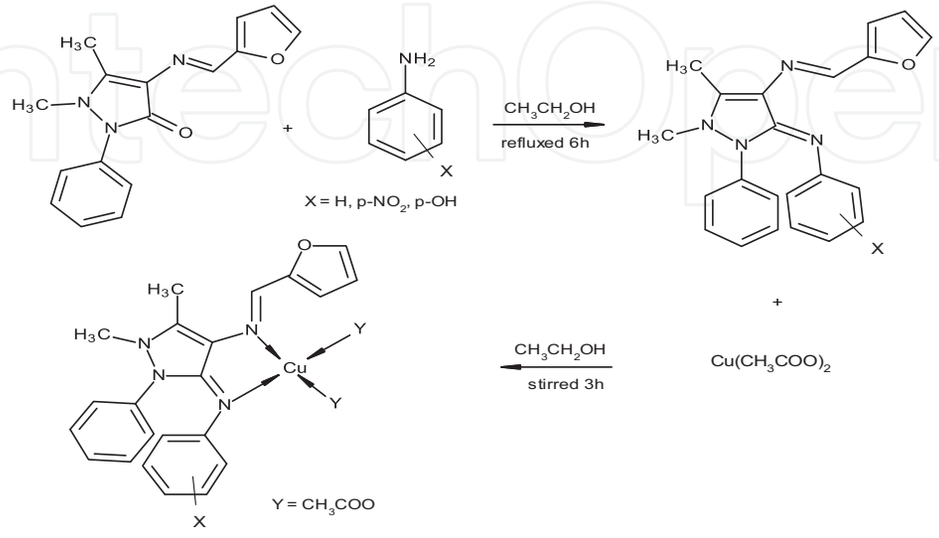

Figure 10. Scheme of synthesis of complexes with ligand **HL**[10].

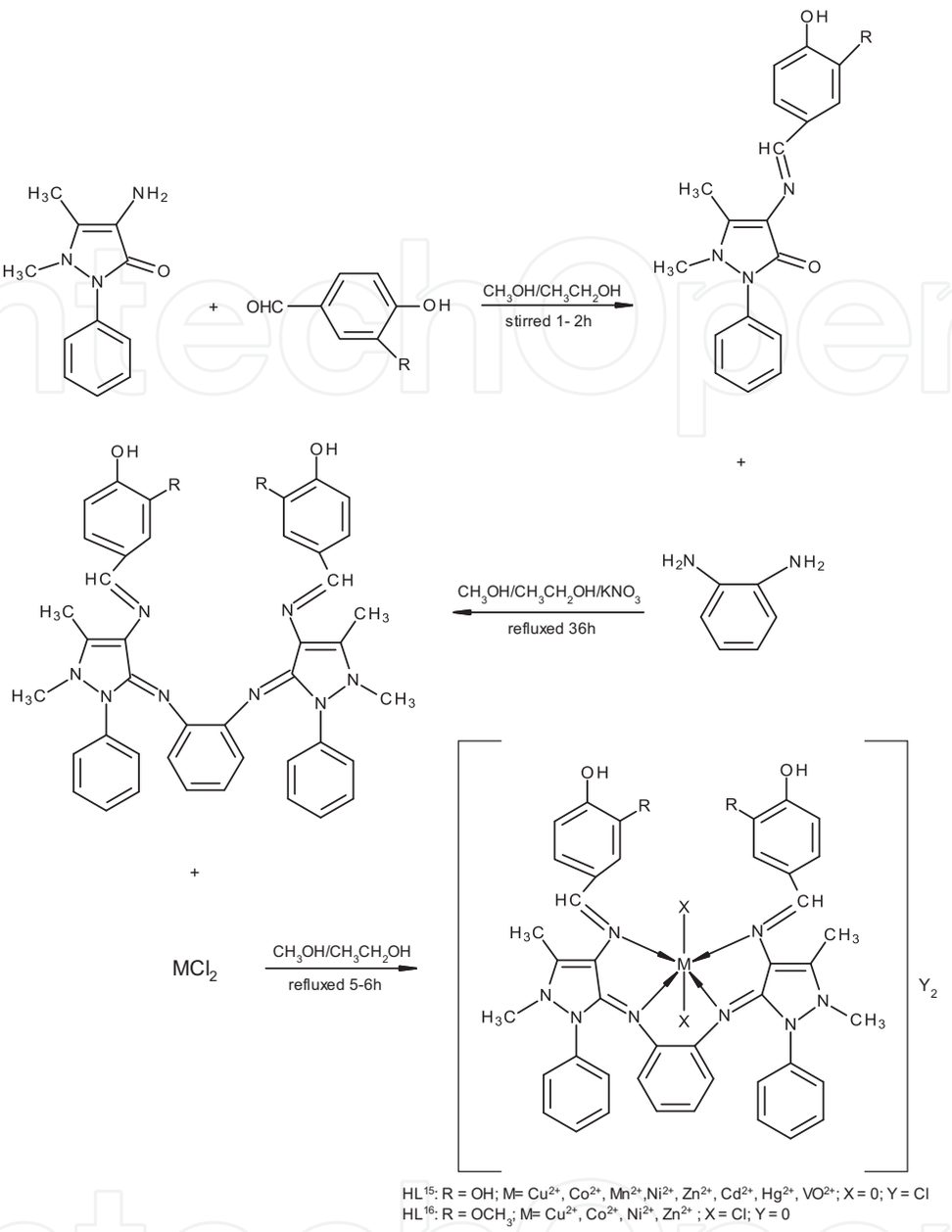

Figure 11. Scheme of synthesis of complexes with ligands **HL**[15] and **HL**[16].

The study methods used to characterize the metal complexes were as follows: elemental analysis, the thermogravimetric analysis, IR, UV-Vis, EPR spectroscopy, the molar electric conductibility, the magnetic susceptibility, and the X-ray diffraction.

2.2.1.1. Synthesis of the complexes with ligand ***HL***[21]

Ligand $C_{24}H_{25}N_3O_4$, (HL^{21})

Ethanolic solution of 3-formyl-6-methyl-chromone (1 mmol) and 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (1 mmol) was stirred at room temperature, then refluxed for 2h, and kept at

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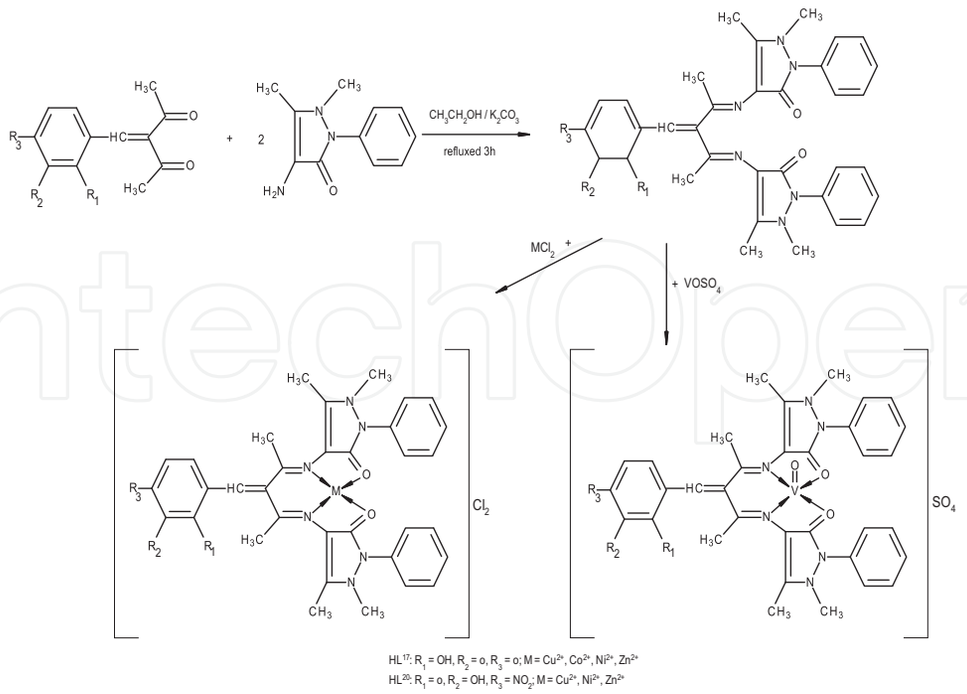

Figure 12. Scheme of synthesis of complexes with ligands **HL**[17] and **HL**[20].

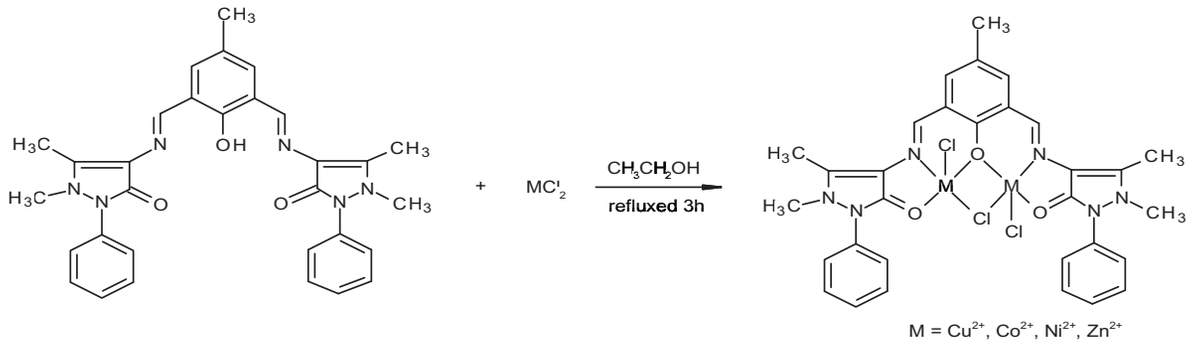

Figure 13. Scheme of synthesis of complexes with ligand **HL**[18].

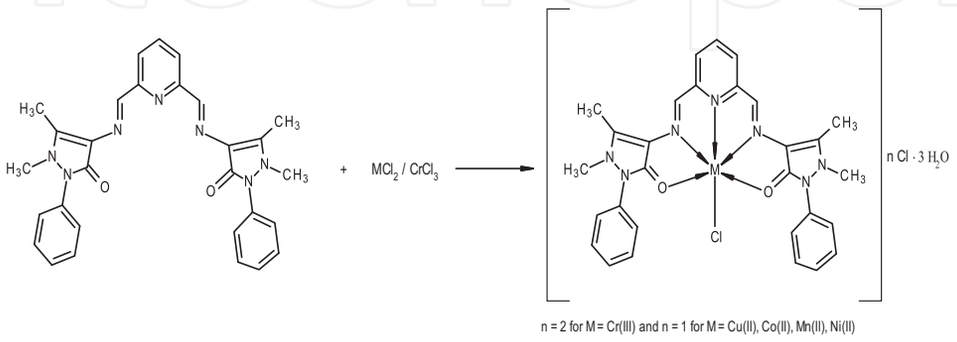

Figure 14. Scheme of synthesis of complexes with ligand **HL**[19].

4°C for 2 days. The resulting precipitate of intense yellow color was filtered, washed with methanol, and dried. Yellow single crystals suitable for structure determination were obtained from methanolic solution upon slow evaporation at room temperature [65].

Complexes **1–3** and **5–9** were prepared by direct reaction between the ligand and the corresponding metal salts, while complex **4** was prepared by the metathetical displacement of the acetate ion, in $Cu(OAc)_2 \cdot H_2O$, by the thiocyanate ion [65] (**Figures 15**, **16**).

$$[\mathbf{Cu_2L^{21}Cl_2}] \quad (1)$$

To $CuCl_2 \cdot 2H_2O$ (2 mmol) dissolved in aqueous/ethanol solution (1:2 v/v) was added ligand $\mathbf{HL^{21}}$ (2 mmol) dissolved in hot ethanol and refluxing for 2 h. The green-brown precipitate, which separated on cooling, was filtered, washed with hot water, ethanol followed by ether, and dried in vacuo.

$$[\mathbf{CuL^{21}(NO_3)}] \quad (2)$$

Complex **2** was prepared similarly, using $Cu(NO_3)_2 \cdot 3H_2O$ (2 mmol). Green solid.

$$[\mathbf{CuL^{21}(OAc)}]\mathbf{CH_3OH} \quad (3)$$

Complex **3** was prepared similarly, using $Cu(OAc)_2 \cdot H_2O$ (2 mmol). Brown solid, X-ray quality single crystals were obtained.

$$[\mathbf{CuL^{21}(SCN)}] \quad (4)$$

For the synthesis of complex **4**, the acetate complex was first prepared and the acetate ion was then displaced by thiocyanate ion by using KSCN (2 mmol). Dark-green solid.

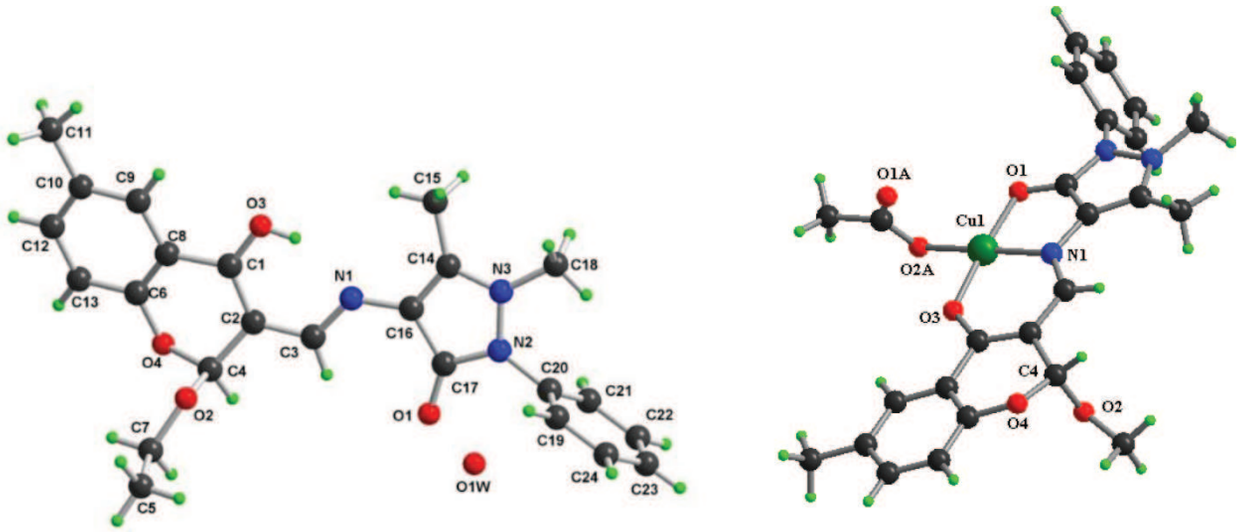

Figure 15. X-ray molecular structure of ligand $\mathbf{HL^{21}}$ and complex **3**.

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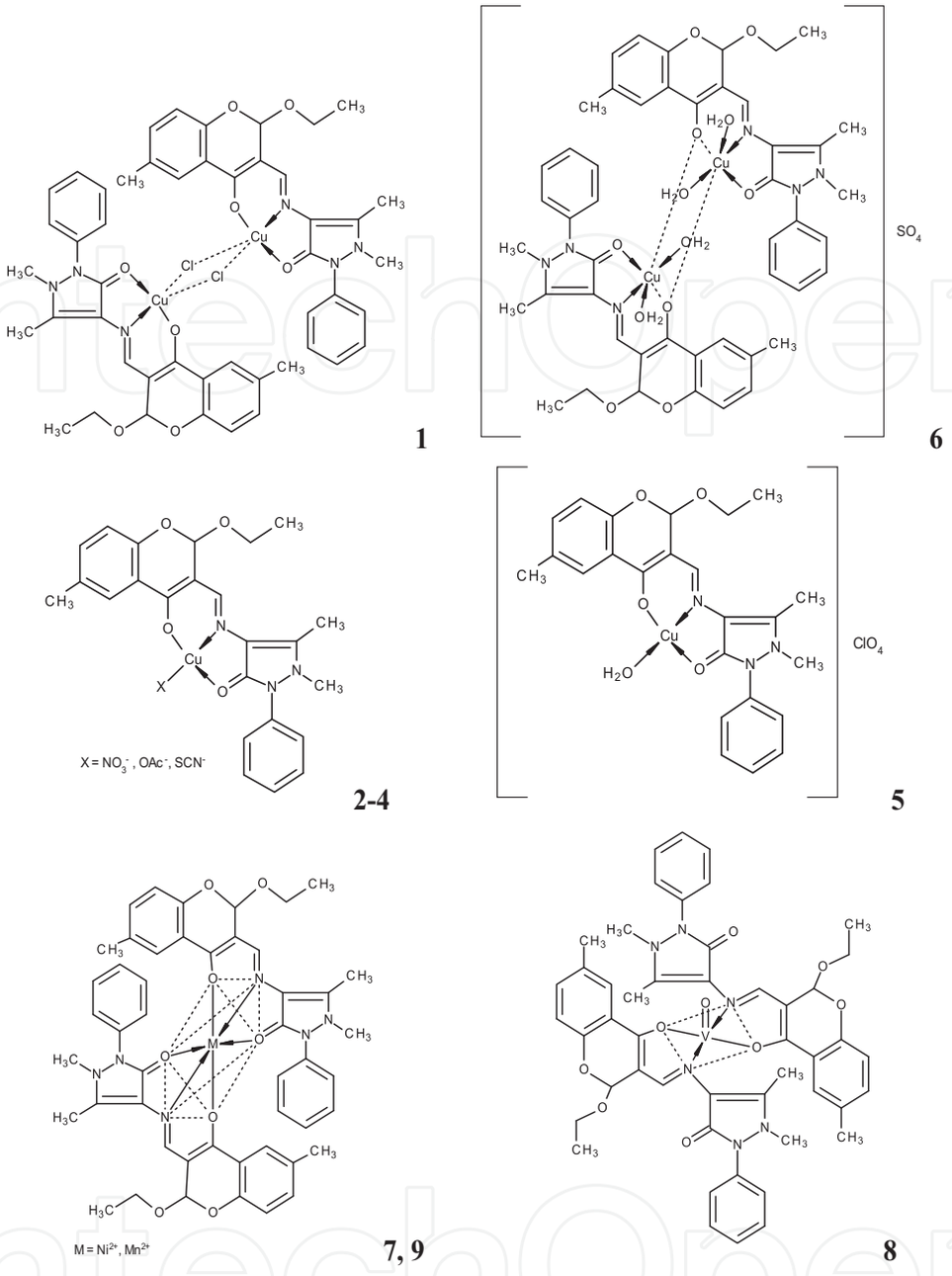

Figure 16. Proposed structures of the metal complexes **1–9**.

$$[\mathbf{CuL}^{21}(\mathbf{H_2O})(\mathbf{ClO_4})] \tag{5}$$

Complex **5** was prepared similarly, using $Cu(ClO_4)_2 \cdot 6H_2O$ (2 mmol). The mixture was stirred at room temperature for 1 h, when a dark-green precipitate appeared immediately.

$$[\mathbf{Cu_2}(\mathbf{L}^{\mathbf{21}})_{\mathbf{2}}(\mathbf{H_2O})_4]\mathbf{SO_4} \tag{6}$$

Complex **6** was prepared similarly, using $CuSO_4 \cdot 5H_2O$ (2 mmol). The mixture was stirred at reflux temperature for 4 h, when appeared a dark-green precipitate.

$$[\mathbf{Ni}(\mathbf{L}^{21})_2] \quad (7)$$

Complex **7** was prepared similarly, using $NiCl_2 \cdot 6H_2O$ (2 mmol). Green to yellow solid.

$$[\mathbf{VO}(\mathbf{L}^{21})_2] \quad (8)$$

Complex **8** was prepared similarly, using $VOSO_4 \cdot 2H_2O$ (2 mmol). Brown solid.

$$[\mathbf{Mn}(\mathbf{L}^{21})_2] \quad (9)$$

Complex **9** was prepared similarly, using $Mn(ClO_4)_2 \cdot 6H_2O$ (2 mmol). Orange solid.

2.2.1.2. Synthesis of the complexes with ligand $\boldsymbol{HL^{22}}$

Ligand $C_{19}H_{19}N_3O_3$, (HL^{22})

The ligand $\mathbf{HL}^{22}$ was synthesized by refluxing equimolar amounts of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 2-hydroxy-4-methoxy-benzaldehyde in ethanol according to the experimental protocol described in Ref. [66].

Complexes **10–12**, **14,** and **15** were prepared by the direct reaction between the ligand and the corresponding metal salts. Complex **13** was obtained by refluxing a mixture of $CuCl_2 \cdot 2H_2O$ and 1-phenyl-2,3-dimethyl-4-(N-2-hydroxy-4-methoxy-benzaldehyde)-3-pyrazolin-5-one with the addition of KSCN (**Figures 17**, **18**) [66].

$$[\mathbf{CuL}^{22}\mathbf{Cl}(\mathbf{H_2O})] \quad (10)$$

An ethanol solution of $CuCl_2 \cdot 2H_2O$ (2 mmol, 15 mL aqueous/ethanol 1:2 v/v) was added dropwise to a stirred ethanol solution of the Schiff base ligand $\mathbf{HL}^{22}$ (2 mmol, 15 mL). The resulting solution was stirring for 3 h at room temperature. The green-brown colored solid was filtered, washed with hot water, ethanol followed by ether, and dried in vacuo.

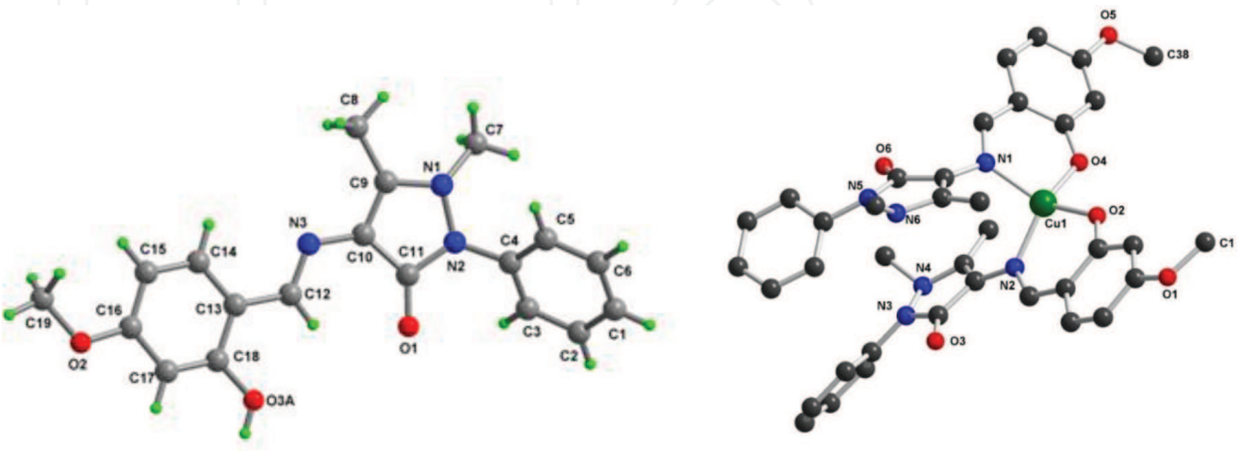

Figure 17. X-ray molecular structure of ligand $\mathbf{HL}^{22}$ and complex **12**.

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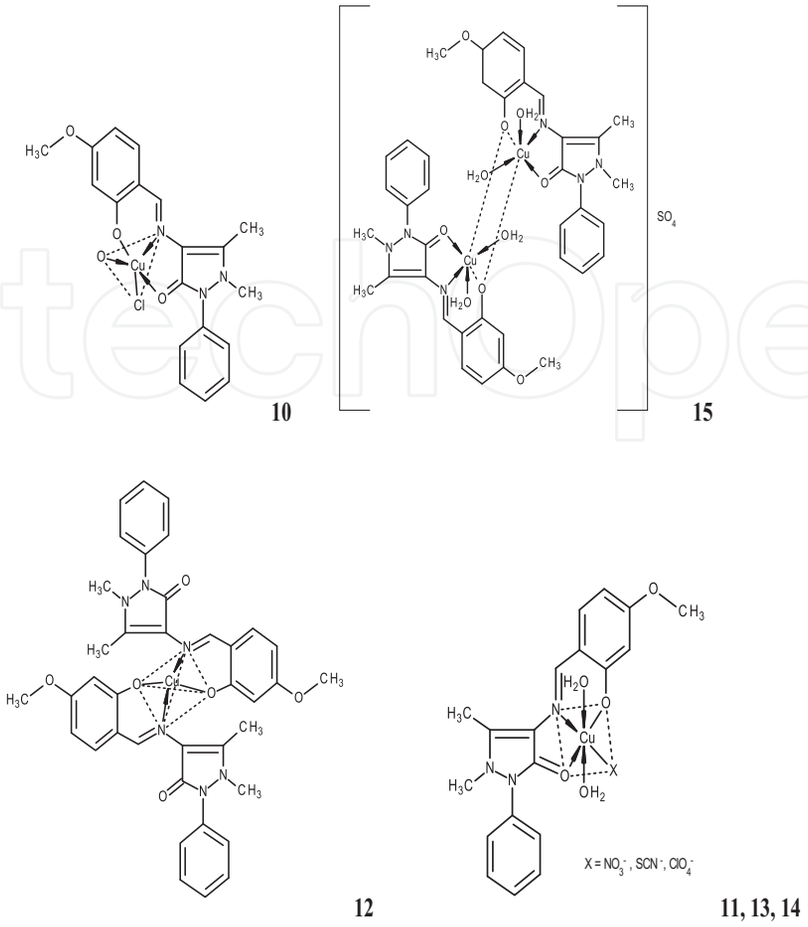

Figure 18. Proposed structures of the metal complexes **10–15**.

$$[\mathbf{CuL^{22}(NO_3)(H_2O)_2}] \tag{11}$$

Complex **11** was prepared similarly, using $Cu(NO_3)_2{\cdot}3H_2O$ (2 mmol). Dark-green solid.

$$[\mathbf{Cu(L^{22})_2}] \tag{12}$$

Complex **12** was prepared similarly, using $Cu(OAc)_2{\cdot}H_2O$ (2 mmol). Brown solid, X-ray quality single crystals were obtained.

$$[\mathbf{CuL^{22}(SCN)(H_2O)_2}] \tag{13}$$

For the synthesis of complex **13**, the chloride complex was first prepared and chloride ion was then displaced by thiocyanate ion by using KSCN (2 mmol). The green colored solid, which separated on cooling, were filtered, washed with hot water, ethanol followed by ether and dried in vacuo.

$$[\mathbf{CuL^{22}(ClO_4)(H_2O)_2}] \tag{14}$$

Complex **14** was prepared similarly, using $Cu(ClO_4)_2{\cdot}6H_2O$ (2 mmol). Green solid.

$$[\mathbf{Cu_2(L^{22})_2(H_2O)_4}]\ \mathbf{SO_4} \tag{15}$$

Complex **15** was prepared similarly, using $CuSO_4 \cdot 5H_2O$ (2 mmol). Dark-green solid.

2.2.1.3. Synthesis of the complexes with ligand $\boldsymbol{HL^{23}}$

Ligand $C_{20}H_{18}N_4O$, (HL^{23})

The ligand $\mathbf{HL^{23}}$ was synthesized by refluxing equimolar amounts of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and indole-3-carboxaldehyde in methanol according to the experimental protocol described in Ref. [67].

Complexes **16–21** were prepared by direct reaction between the ligand and the corresponding metal salts (**Figures 19**, **20**) [67].

$$[\mathbf{Cu(L^{23})_2Cl_2}] \tag{16}$$

To a stirred solution of $CuCl_2 \cdot 2H_2O$ (1 mmol) in ethanol (15 mL) was added a solution of ligand $\mathbf{HL^{23}}$ (1 mmol) in ethanol (15 mL). The mixture was stirred at reflux temperature for 2 h. The resulting precipitate of green-brown color was filtered, washed with ethanol, and dried.

$$[\mathbf{Cu(L^{23})_2}]\ (\mathbf{NO_3})_2 \tag{17}$$

Complex **17** was prepared similarly, using $Cu(NO_3)_2 \cdot 3H_2O$ (1 mmol). Brown solid.

$$[\mathbf{Cu(L^{23})_2(OAc)_2}] \tag{18}$$

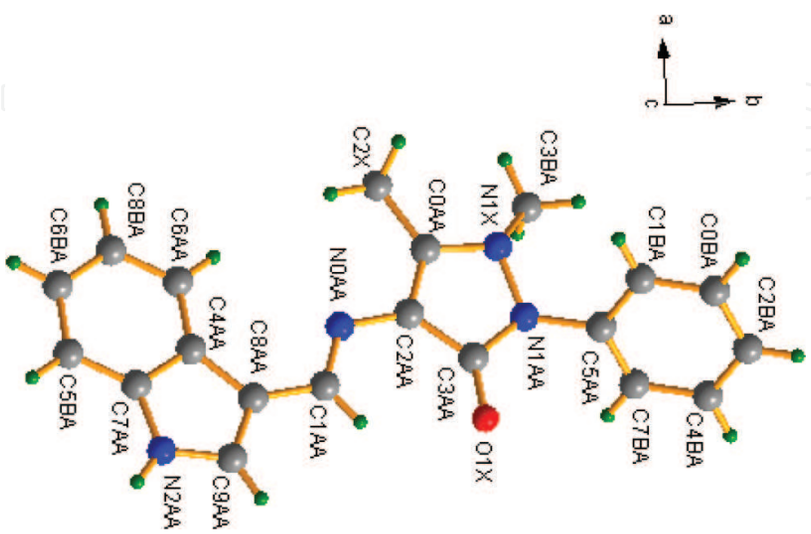

Figure 19. X-ray molecular structure of ligand $\mathbf{HL^{23}}$.

http://dx.doi.org/10.5772/67584

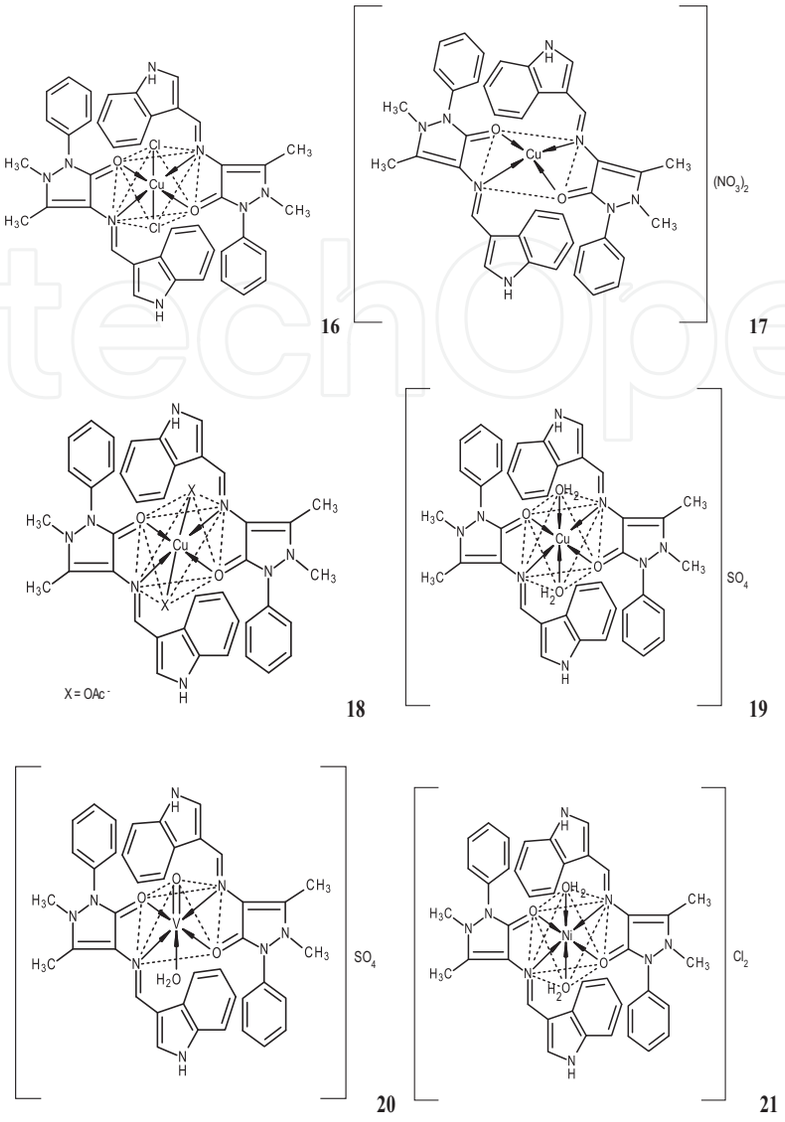

Figure 20. Proposed structures of the metal complexes **16–21**.

Complex **18** was prepared similarly, using $Cu(OAc)_2 \cdot H_2O$ (1 mmol). Dark-green solid.

$$[\mathbf{Cu}(\mathbf{L}^{23})_2(\mathbf{H_2O})_2]\ \mathbf{SO_4} \tag{19}$$

Complex **15** was prepared similarly, using $CuSO_4 \cdot 5H_2O$ (1 mmol). Green solid.

$$[\mathbf{VO}(\mathbf{L}^{23})_2(\mathbf{H_2O})]\ \mathbf{SO_4} \tag{20}$$

Complex **20** was prepared in a similarly, using $VOSO_4 \cdot 2H_2O$. Green solid.

$$[\mathbf{Ni}(\mathbf{L}^{23})_2(\mathbf{H_2O})_2]\mathbf{Cl_2} \tag{21}$$

Complex **21** was prepared in a similarly, using $NiCl_2 \cdot 6H_2O$. Dark-green solid.

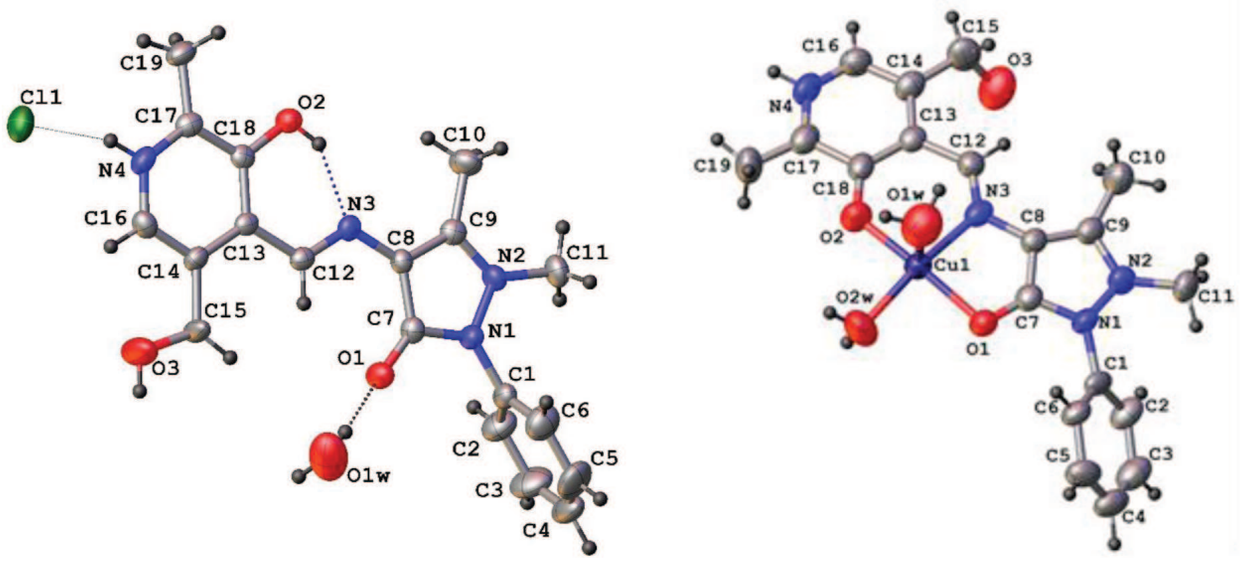

Figure 21. X-ray molecular structure of ligand $\mathbf{HL}^{24}$ and complex **23**.

2.2.1.4. Synthesis of the complexes with ligand $\boldsymbol{HL^{24}}$

Ligand $C_{19}H_{20}N_4O_3$, ($\mathbf{HL}^{24}$)

The ligand $\mathbf{HL}^{24}$ was synthesized by refluxing equimolar amounts of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and pyridoxal hydrochloride in methanol according to the experimental protocol described in Ref. [68].

Complexes **22–28** were prepared by direct reaction between the ligand and the corresponding metal salts (**Figures 21**, **22**) [68].

$$[\mathbf{CuL}^{24}\mathbf{Cl}]_2 \tag{22}$$

To a hot solution of $\mathbf{HL}^{24}$ (1 mmol) in methanol was added a hot solution of $CuCl_2{\cdot}2H_2O$ (2 mmol) in aqueous/methanol (1:2 v/v), and the mixture was stirred at reflux temperature for 4h. Brown solid.

$$[\mathbf{CuL}^{24}(\mathbf{H_2O})_2]\ \mathbf{NO_3}\cdot\mathbf{2.25H_2O} \tag{23}$$

Complex **23** was prepared similarly, using $Cu(NO_3)_2{\cdot}3H_2O$ (1 mmol). The mixture was stirred at room temperature for 7h. Brown solid, X-ray quality single crystals were obtained.

$$[\mathbf{Cu}(\mathbf{L}^{24})(\mathbf{OAc})(\mathbf{H_2O})] \tag{24}$$

Complex **24** was prepared similarly, using $Cu(OAc)_2{\cdot}H_2O$ (2 mmol). The mixture was stirred at reflux temperature for 4h. Green-brown solid.

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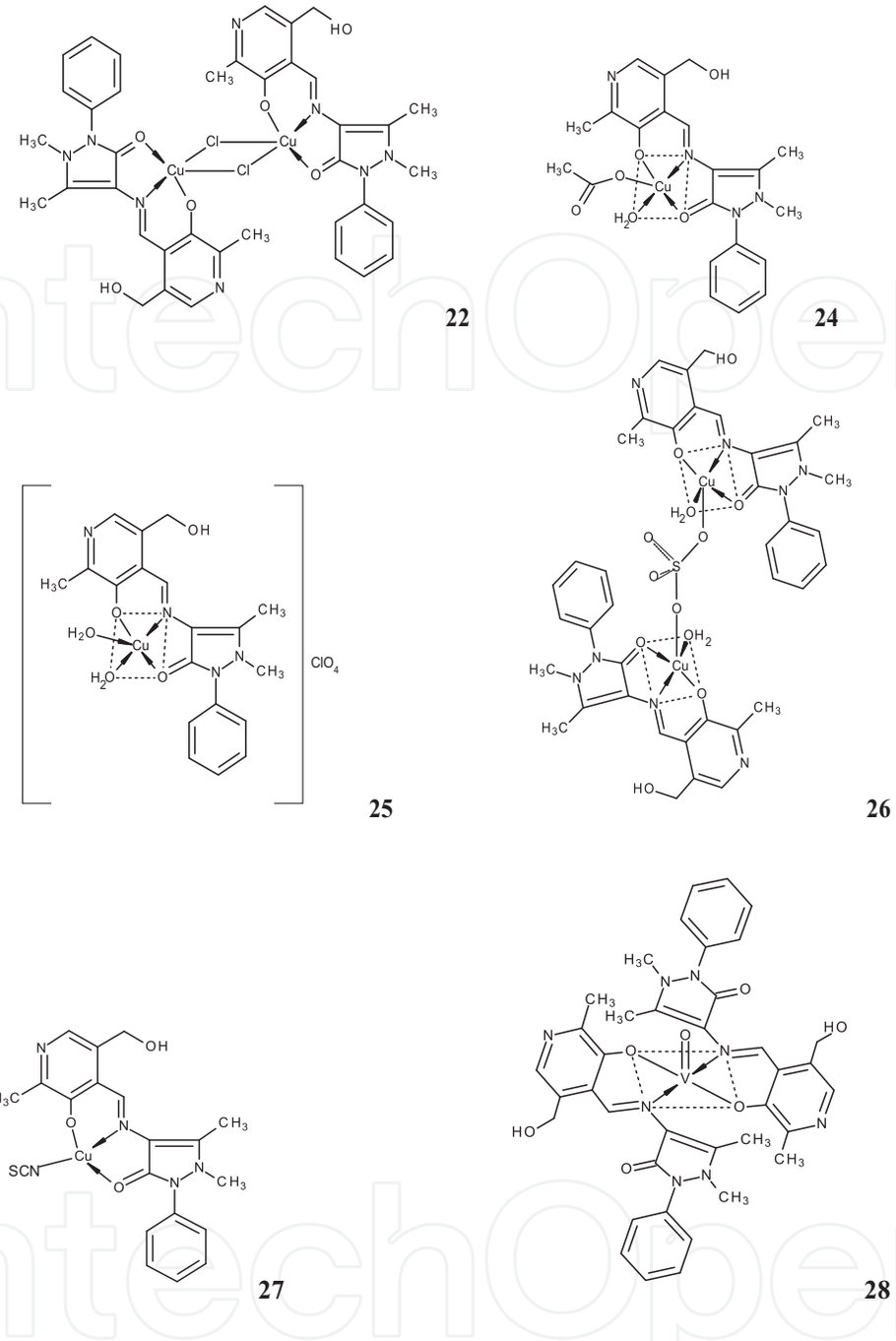

Figure 22. Proposed structures of the metal complexes **22**, **24–28**.

$$[\mathbf{CuL^{24}(H_2O)_2}]\ \mathbf{ClO_4} \tag{25}$$

Complex **25** was prepared similarly, using $Cu(ClO_4)_2{\cdot}6H_2O$ (2mmol). The mixture was stirred at reflux temperature for 5h. Brown solid.

$$[\mathbf{Cu_2(L^{24})_2(SO_4)(H_2O)_2}] \tag{26}$$

Complex **26** was prepared in a similar fashion to complex **24**, using $CuSO_4 \cdot 5H_2O$. The mixture was stirred at reflux temperature for 4h, giving a dark-red precipitate.

$$[\mathbf{CuL^{24}(NCS)}] \cdot \mathbf{2H_2O} \tag{27}$$

For the synthesis of complex **27**, the acetate complex was first prepared and the acetate ion was then displaced by thiocyanate ion by using KSCN (2mmol). Green solid.

$$[\mathbf{VO(L^{24})_2}] \tag{28}$$

Complex **28** was prepared in a similar fashion to complex **24**, using $VOSO_4 \cdot 2H_2O$. Brown solid.

2.3. Antibacterial activity

The complexes and ligands $\mathbf{HL^{21–24}}$ were tested for their in vitro antibacterial activity against de *Staphylococcus aureus var. Oxford 6538, Klebsiella pneumoniae ATCC* 100131, *Escherichia coli ATCC 10536,* and *Pseudomonas aeruginosa ATCC 9027* strains using the paper disc diffusion method (for the qualitative determination) and the serial dilutions in liquid broth method (for determination of MIC) [66]. Streptomycin was used as internal standard.

The results of the antibacterial activity point out the fact that the activity of the Schiff bases $\mathbf{HL^{21–24}}$ is more pronounced when it coordinates at the metal ion (**Table 1**). In case of complexes **1**, **6**, **10**, **12**, **15**, **18**, **19**, **20**, **23**, **25**, **26,** and **28,** there can be seen a visible increase in the antibacterial action.

Missing a clear action mechanism, in vitro, of the respective ligand of the complexes obtained on a microbian stem, there can be made the following stipulations:

-the structure of the tested complexes seems to be the main element that influences the antibacterial activity. Thus, for complexes **1**, **6**, **10**, **12**, **15**, **19**, **20**, **23**, **25**, **26,** and **28,** there has been determined an increased activity against all bacterial species, probably due to the presence of the monomeric form in DMSO solution and also due to the tetracoordination of the metal center.

-the presence of the anions with a large volume, in the outer coordination sphere of the complexes, can be deemed as another main element that can influence the antibacterial activity. The complexes **5**, **6**, **15**, **19**, **20**, and **25** contain the groups ClO_4^- and SO_4^{2-}, respectively, and prevent a visible increase in their activity against all species of bacteria used.

-if there is drawn a comparison between the coefficients of the molecular orbitals, computed on the basis of the transitions noticed in spectra UV-Vis and of the parameters g and A in spectra EPR [69] and the antibacterial activity, the conclusion is the fact that, for the complexes with the most pronounced activity, the values of δ^2 parameter to a weak covalent character of the link π out of the plan.

	Minimum inhibitory concentration (μg/ml)			
Compusul	***K. pneumoniae G(+)***	***S. aureus G(+)***	***P. aeruginosa G(−)***	***E. coli G(−)***
HL^{21}	256	256	512	128
$[Cu_2(L^{21})_2(Cl)_2]$ **(1)**	32	8	32	32
$[CuL^{21}(NO_3)]$ **(2)**	64	32	256	512
$[CuL^{21}(OAc)]$ **(3)**	64	32	256	512
$[CuL^{21}(SCN)]$ **(4)**	64	32	256	512
$[CuL^{21}(H_2O)]ClO_4$ **(5)**	32	32	128	256
$[Cu_2(L^{21})_2(H_2O)_4]SO_4$ **(6)**	16	8	32	32
$[Ni(L^{21})_2]$ **(7)**	512	512	256	512
$[VO(L^{21})_2]$ **(8)**	265	256	64	256
$[Mn(L^{21})_2]$ **(9)**	256	512	256	128
HL^{22}	128	256	256	512
$[Cu(L^{22})Cl(H_2O)]$ **(10)**	16	8	128	16
$[Cu(L^{22})(NO_3)(H_2O)_2]$ **(11)**	128	128	256	256
$[Cu(L^{22})_2]$ **(12)**	8	4	16	64
$[CuL^{22}(SCN)(H_2O)_2]$ **(13)**	64	64	256	512
$[CuL^{22}(ClO_4)(H_2O)_2]$ **(14)**	256	128	256	512
$[Cu_2(L^{22})_2(H_2O)_4]SO_4$ **(15)**	8	16	128	16
HL^{23}	64	128	64	32
$[Cu(L^{23})_2Cl_2]$ (**16**)	64	128	64	64
$[Cu(L^{23})_2](NO_3)_2$ (**17**)	128	64	32	64
$[Cu(L^{23})_2(OAc)_2]$ **(18)**	8	4	16	16
$[Cu(L^{23})_2(H_2O)_2]SO_4$ (**19**)	8	8	64	16
$[VO(L^{23})_2(H_2O)]SO_4$ (**20**)	64	128	16	256
$[Ni(L^{23})_2(H_2O)_2]Cl_2$ **(21)**	256	256	256	128
HL^{24}	128	256	256	512
$[CuL^{24}Cl]_2$ (**22**)	64	64	256	512
$[CuL^{24}(H_2O)_2]NO_3{\cdot}2.25H_2O$ (**23**)	16	8	128	16
$[Cu(L^{24})(OAc)(H_2O)]$ (**24**)	128	128	256	256
$[CuL^{24}(H_2O)_2]\ ClO_4$ (**25**)	8	4	16	64
$[Cu_2(L^{24})_2(SO_4)(H_2O)_2]$ (**26**)	8	64	16	64
$[CuL^{24}(NCS)]{\cdot}2H_2O$ (**27**)	256	128	256	512
$[VO(L^{24})_2]$ (**28**)	8	16	128	16
Streptomycin	8	4	16	8

K. pneumoniae (*Klebsiella pneumoniae* ATCC 31488); *S. aureus* (*Staphylococus aureus* var. Oxford ATCC 6538); *P. aeruginosa* (*Pseudomonas aeruginosa* ATCC 9027); *E. coli* (*Escherichia coli* ATCC 10536). G(−): Gram-negative bacteria; G(+): Gram-positive bacteria.

Table 1. "*In vitro*" antibacterial activity of the ligands and corresponding complexes.

3. Conclusion

The investigations of the antibacterial screening, carried out for these new classes of compounds, reveal the fact that they present activity, especially toward the gram-positive bacteria, in comparison with the standard streptomycin. The increased antibacterial activity of the metal complexes can be accounted for by a cluster of reasons that refer to the chelation theory, nature of the ligand and of the metal ion, the geometry of the metal complexes, liposolubility, the presence of the co-ligands, and a series of sterical and pharmacokinetic factors. We can say that, ten of the complexes synthetized can be successfully used instead of streptomycin, where there is resistance to this antibiotic.

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References

[1] Baquero F., Gram-positive resistance: challenge for the development of new antibiotics. Journal of Antimicrobial Chemotherapy. 1997; **39**: 1–6.

[2] Alekshun M.N., Levy S.B., Molecular mechanisms of antibacterial Multidrug resistance. Cell. 2007; **128**: 1037–1050.

[3] Rice L.B., Unmet medical needs in antibacterial therapy. Biochemical Pharmacology. 2006; **71**: 991–995.

[4] Dhar D.N., Taploo C.L., Schiff bases and their applications. Journal of Scientific and Industrial Research. 1982; **41**: 501–506.

[5] Przybylski P., Huczynski A., Pyta K., Brzezinski B., Bartl F., Biological properties of Schiff bases and azo derivatives of phenols. Current Organic Chemistry. 2009; **13**: 124–148.

[6] Wang P.H., Keck J.G., Lien E.J., Lai M.M.C., Design, synthesis, testing, and quantitative structure-activity relationship analysis of substituted salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus. Journal of Medicinal Chemistry. 1990; **33**: 608–614.

[7] Jarrahpour A., Motamedifar M., Pakshir K., Hadi N., Zarei M., Synthesis of novel azo Schiff bases and their antibacterial and antifungal activities. Molecules. 2004; **9**: 815–824.

[8] Ceyhana G., Urus S., Demirtas I., Elmastas M., Tumera M., Antioxidant, electrochemical, thermal, antimicrobial and alkane oxidation properties of tridentate Schiff base ligands and their metal complexes. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2011; **81**:184–198.

[9] Xiong Y.Z., Chen F.E., Balzarini J., Clercq E.D., Pannecouque C., Non-nucleoside HIV-1 reverse transcriptase inhibitors. Part 11: Structural modulations of diaryltriazines with potent anti-HIV activity. European Journal of Medicinal Chemistry. 2008; **43**: 1230–1236.

[10] Sriram D., Yogeeswari P., Sirisha N., Saraswat V., Abacavir prodrugs: Microwave-assisted synthesis and their evaluation of anti-HIV activities. Bioorganic & Medicinal Chemistry Letters. 2006; **16**: 2127–2129.

[11] Bhandari S.V., Bothara K.G., Raut M.K., Patil A.A., Sarkate A.P., Mokale V.J., Design, synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel s-substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives. Bioorganic & Medicinal Chemistry. 2008; **16**: 1822–1831.

[12] Sridhar K., Pandeya N., Stables P., Ramesh A., Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives. European Journal of Pharmaceutical Sciences. 2002; **16**:129–132.

[13] Kaplan J.P., Raizon B.M., Desarmenien M., Feltz P., Headley P.M., Worms P., Lloyd K.G., Bartholini G., New anticonvulsants: Schiff bases of.gamma.-aminobutyric acid and. gamma.-aminobutyramide. Journal of Medicinal Chemistry. 1980; **23**: 702–704.

[14] Das A., Trousdale M.D., Ren S., Lien E.J., Inhibition of herpes simplex virus type 1 and adenovirus type 5 by heterocyclic Schiff bases of aminohydroxyguanidine tosylate. Antiviral Research. 1999; **44**: 201–208.

[15] Mladenova R., Ignatova M., Manolova N., Petrova T., Rashkov I., Preparation, characterization and biological activity of Schiff base compounds derived from 8-hydroxyquinoline-2-carboxaldehyde and Jeffamines ED. European Polymer Journal. 2002; **38**: 989–1000.

[16] Walsh O.M., Meegan M.J., Prendergast R.M., Nakib T.A., Synthesis of 3-acetoxyazetidin-2-ones and 3-hydroxyazetidin-2-ones with antifungal and antibacterial activity. European Journal of Medicinal Chemistry. 1996; **31**: 989–1000.

[17] Liu Y., Yang Z., Synthesis, crystal structure, antioxidation and DNA binding properties of binuclear Ho(III) complexes of Schiff-base ligands derived from 8-hydroxyquinoline-2 carboxy-aldehyde and four aroyl-hydrazines. Journal of Organometallic Chemistry. 2009; **694**: 3091–3101.

[18] Bringmann G., Dreyer M., Faber J.H., Dalsgaard P.W., Staerk D., Jaroszewski J.W., Ndangalasi F., Mbago R., Brun S., Brøgger C., Ancistrotanzanine C and related 5,1′- and 7,3′-coupled naphthyliso-quinoline alkaloids from *Ancistrocladus tanzaniensis*. Journal of Natural Products. 2004; **67**:743–748.

[19] Rehman W., Baloch M.K., Muhammad B., Badshah A., Khan K.M., Characteristic spectral studies and in vitro antifungal activity of some Schiff bases and their organotin(IV) complexes. Chinese Science Bulletin. 2004; **49**:119–22.

[20] Guo Z., Xing R., Liu S., Zhong Z., Ji X., Wang L., Pengcheng L., Antifungal properties of Schiff bases of chitosan, N-substituted chitosan and quaternized chitosan. Carbohydrate Research. 2007; **342**: 1329–1332.

[21] Souza A.O., Galetti F.C.S., Silva C.L., Bicalho B., Parma M.M., Fonseca S.F., Marsaioli A.J., Trindade A.C.L.B., Gil R.P.F., Bezerra F.S., Andrade-Neto M., Oliveira M.C.F., Antimycobacterial and cytotoxicity activity of synthetic and natural compounds. Química Nova. 2007; **30**: 1563–1566.

[22] Shi L., Ge H.M., Tan S.H., Li H.Q., Song Y.C., Zhu H.L., Tan R.X., Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde. European Journal of Medicinal Chemistry. 2007; **42**: 558–564.

[23] Pandeya S.N., Sriram D., Nath G., De Clercq E., Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. IL Farmaco. 1999; **54**: 624–628.

[24] Jarrahpour A., Khalili D., De Clercq E., Salmi C., Brunel J.M., Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. Molecules. 2007; **12**: 1720–1730.

[25] Hearn M.J., Cynamon M.H., Design and synthesis of antituberculars: preparation and evaluation against *Mycobacterium tuberculosis* of an isoniazid Schiff base. Journal of Antimicrobial Chemotherapy. 2004; **53**: 185–191.

[26] Karthikeyan M.S., Prasad D.J., Poojary B., Bhat K.S., Holla B.S., Kumari N.S., Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorganic & Medicinal Chemistry. 2006; **14**: 7482–7489.

[27] Chandra S., Synthesis of new fungicides. 2-(4′-Arylthiazolyl-2'-imino)-3-aryl-4-thiazolidones. Bulletin of the Chemical Society of Japan. 1967; **40**: 2422–2424.

[28] Modi D., Sabnis S.S., Deliwala C.V., Potential anticancer agents. III. Schiff bases from benzaldehyde nitrogen mustards and aminophenylthiazoles. Journal of Medicinal Chemistry.1970; **13**: 935–941.

[29] Johnson D.K., Murphy T.B., Rose T.B., Goodwin W.H., Pickart L., Cytotoxic chelators and chelates. Inhibition of DNA synthesis in cultured rodent and human cells by aroylhydrazones and by a copper(II) complex of salicylaldehyde benzoyl hydrazone. Inorganica Chimica Acta. 1982; **67**: 159–165.

[30] Knorr L.On the constitution of quinizine derivatives. Reports of the German Chemical Society (A and B Series). 1883; **17**: 2032–2049.

[31] Girges M.M, Abou El-Zahab M.M, Hanna M.A, Synthesis of novel 4-substituted phenazone derivatives as potential antibacterial and antineoplastic agents. Archives of Pharmacal Research. 1988; **11**: 169–174.

[32] Rubtsov A.E., Makhmudov R.R., Kovylyaeva N.V., Prosyanik N.I., Bobrov A.V., Zalesov V.V., Synthesis, antiinflammatory and analgesic activity of 4-antipyrine derivatives. Pharmaceutical Chemistry Journal. 2002; **36**: 608–612.

[33] Ito T., Goto C., Noguchi K. Lanthanoid ion-selective solvent polymeric membrane electrode based on 1-phenyl-3-methyl-4-octadecanoyl-5-pyrazolone. Analytica Chimica Acta. 2001; **443**: 41–51.

[34] Radzikowska E., Onish K., Chojak E., Prospective assessment of cancer incidence and antipyrine metabolism. European Journal of Cancer. 1995; **31**: S225.

[35] Ismail M.M.F., Ammar Y.A., El-Zahaby H.S.A., Eisa S.I., Barakat S.E.S., Synthesis of novel 1-pyrazolylpyridin-2-ones as potential anti-inflammatory and analgesic agents. Archiv der Pharmazie – Chemistry in Life Sciences. 2007; **340**: 476–482.

[36] Mahmoud M., Abdel-Kader R., Hassanein M., Saleh S., Botros S., Antipyrine clearance in comparison to conventional liver function tests in hepatitis C virus patients. European Journal of Pharmacology. 2007; **569**: 222–227.

[37] Sondhi S.M., Sharma V.K., Verma R.P., Singhal N., Shukla R., Raghubir R., Dubey M.P., Synthesis, anti-inflammatory and analgesic activity evaluation of some mercapto pyrimidine and pyrimidobenzimidazole derivatives. Synthesis-Stuttgart. 1999; **5**: 878–884.

[38] Sondhi S.M., Singhal N., Verma R.P., Arora S.K., Dastidar S.G., Synthesis of hemin and porphyrin derivatives and their evaluation for anticancer activity. Indian Journal of Chemistry Section B Organic and Medicinal Chemistry. 2001; **40**: 113–119.

[39] Bondock S., Rabie R., Etman H.A., Fadda A.A., Synthesis and antimicrobial activity of some new heterocycles incorporating antipyrine moiety. European Journal of Medicinal Chemistry. 2008; **43**: 2122–2129.

[40] Cunha S., Oliveira S.M., Rodrigues M.T., Bastos R.M., Ferrari J., Oliveira C.M.A., Kato L., Napolitano H.B., Vencato I., Lariucci C., Structural studies of 4-aminoantipyrine derivatives. Journal of Molecular Structure, 2005; **752**: 32–39.

[41] Mishra A.P., Physicochemical and antimicrobial studies on nickel(II) and copper(II) Schiff base complexes derived from 2-furfuraldehyde. Journal of the Indian Chemical Society. 1999; **76**: 35–37.

[42] Raman N., Kulandaisamy A., Jeyasubramanian K., Synthesis, spectral, redox, and antimicrobial activity of Schiff base transition metal(II) complexes derived from 4-aminoantipyrine and benzil. Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry. 2002; **32**: 1583–1610.

[43] Raman N., Kulandaisamy A., Shunmugasundaram A., Jeyasubramanian K., Synthesis, spectral, redox and antimicrobial activities of Schiff base complexes derived from 1-phenyl-2,3-dimethyl-4-aminopyrazol-5-one and acetoacetanilide. Transition Metal Chemistry. 2001; **26**: 131–135.

[44] Anupama B., Kumari G.C., Synthesis, characterization, DNA binding and antimicrobial activity of 4-amino antipyrine Schiff base metal complexes. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011; **2**: 140–159.

[45] Ispir E., Toroğlu S., Kayraldiz A., Syntheses, characterization, antimicrobial and genotoxic activities of new Schiff bases and their complexes. Transition Metal Chemistry. 2008; **33**: 953–960.

[46] Anitha C., Sheela C.D., Tharmaraj P., Sumathi S., Spectroscopic studies and biological evaluation of some transition metal complexes of azo Schiff-base ligand derived from (1-phenyl-2,3-dimethyl-4-aminopyrazol-5-one) and 5-((4-chlorophenyl)diazenyl)-2 hydroxybenzaldehyde. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2012; **96**: 493–500.

[47] Selwin Joseyphus R., Shiju C., Joseph J., Justin Dhanaraj C., Arish D., Synthesis and characterization of metal complexes of Schiff base ligand derived from imidazole-2-carboxaldehyde and 4-aminoantipyrine. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2014; **133**: 149–155.

[48] Ismail Kamal Z., Synthesis, spectroscopic, magnetic and biological activity studies of copper(II) complexes of an antipyrine Schiff base. Transition Metal Chemistry. 2000; **25**: 522–528.

[49] Raman N., Johnson Raja S., Joseph J., Dhaveethu Raja J., Molecular designing, structural elucidation, and comparison of the cleavage ability of oxovanadium(IV) Schiff Base Complexes. Russian Journal of Coordination Chemistry. 2007; **33**: 7–11.

[50] Joseph J., Ayisha Bibin Rani G., Metal based SOD mimetic therapeutic agents: synthesis, characterization and biochemical studies of metal complexes. Arabian Journal of Chemistry. 2013; **6**: 1–9.

[51] Joseph J., Ayisha Bibin Rani G., Antioxidant and biochemical activities of mixed ligand complexes. Applied Biochemistry and Biotechnology. 2014; **172**: 867–890.

[52] Sakthivel A., Raman N., Mitu L., DNA interaction studies of pyrazolone- and diimine-incorporated Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) complexes: synthesis, spectroscopic characterization, and antimicrobial study. Monatshefte für Chemie. 2013; **144**: 605–620.

[53] Raman N., Sakthivel A., Selvaganapathy M., Mitu L., Effect of DNA interaction involving antioxidative 4-aminoantipyrine incorporating mixed ligand complexes having alpha-amino acid as co-ligand. Journal of Molecular Structure. 2013; **1060**: 63–74.

[54] Shiva Leela D., Ushaiah B., Anupama G., Sunitha M., Gyana Kumari C., Synthesis, characterization, antimicrobial, DNA binding and cleavage studies of mixed ligand Cu (II), Co(II) complexes. Journal of Fluorescence. 2015; **25**: 185–197.

[55] Raman N., Kulandaisamy A., Thangaraja C., Manisankar P., Viswanathan S., Vedhi C., Synthesis, structural characterisation and electrochemical and antibacterial studies of Schiff base copper complexes. Transition Metal Chemistry. 2004; **29**: 129–135.

[56] Raman N., Johnson Raja S., Joseph J., Dhaveethu Raja J., Synthesis, spectral characterization and DNA cleavage study of heterocyclic Schiff base metal complexes. Journal of the Chilean Chemical Society. 2007b; **52**: 1138–1141.

[57] Joseph J., Nagashri K., Ayisha Bibin Rani G., Synthesis, characterization and antimicrobial activities of copper complexes derived from 4-amino-antipyrine derivatives. Journal of Saudi Chemical Society. 2013; **17**: 285–294.

[58] Kavitha T., Kulandaisamy A., Thillaiarasu P., Synthesis, spectroscopic characterization, electrochemical and antimicrobial studies of copper(II), nickel(II), cobalt(II), zinc(II) and oxovanadium(II) complexes derived from napthylidene-4-aminoantipyrine and tryptophan. International Journal of Innovative Research in Science, Engineering and Technology. 2015; **4**: 12221–12231.

[59] Raman N., Dhaveethu Raja J., Sakthivel A., Synthesis, spectral characterization of Schiff base transition metal complexes: DNA cleavage and antimicrobial activity studies. Journal of Chemical Sciences. 2007c; **119**: 303–310.

[60] Sivasankaran Nair M., Arish D., Synthesis, characterization and biological studies of Co (II), Ni(II), Cu(II) and Zn(II) complexes involving a potentially tetradentate Schiff base ligand. Transactions of the Indian Institute of Metals. 2011; **64**: 287–292.

[61] Raman N., Thangaraja C., Johnsonraja S., Synthesis, spectral characterization, redox and antimicrobial activity of Schiff base transition metal(II) complexes derived from 4-aminoantipyrine and 3-salicylidene-acetylacetone. Central European Journal of Chemistry. 2005; **3**: 537–555.

[62] Annigeri S.M., Sathisha M.P., Revankar V.K., Spectroscopic studies of bridged binuclear complexes of Co(II), Ni(II), Cu(II) and Zn(II). Transition Metal Chemistry. 2007; **32**: 81–87.

[63] Raman N., Mitu L., Sakthivel A., Pandi M.S.S., Studies on DNA cleavage and antimicrobial screening of transition metal complexes of 4-amino-antipyrine derivatives of N_2O_2 type. Journal of the Iranian Chemical Society. 2009; **6**: 738–748.

[64] Rosu T., Negoiu M., Pasculescu S., Pahontu E., Poirier D., Gulea A., Metal-based biologically active agents: synthesis, characterization, antibacterial and antileukemia activity evaluation of Cu(II), V(IV) and Ni(II) complexes with antipyrine-derived compounds. European Journal of Medicinal Chemistry. 2010; **45**: 774–781.

[65] Rosu T., Pahontu E., Maxim C., Georgescu R., Stanica N., Almajan G.L., Gulea A., Synthesis, characterization and antibacterial activity of some new complexes of Cu(II), Ni(II), VO(II), Mn(II) with Schiff base derived from 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one. Polyhedron. 2010; **29**: 757–766.

[66] Rosu T., Pahontu E., Maxim C., Georgescu R., Stanica N., Gulea A., Some new Cu(II) complexes containing an ON donor Schiff base: Synthesis, characterization and antibacterial activity. Polyhedron. 2011; **30**: 154–162.

[67] Rosu T., Pahontu E., Ilies D.-C., Georgescu R., Mocanu M., Leabu M., Shova S., Gulea A., Synthesis and characterization of some new complexes of Cu(II), Ni(II) and V(IV) with Schiff base derived from indole-3-carboxaldehyde. Biological activity on prokaryotes and eukaryotes. European Journal of Medicinal Chemistry. 2012; **53**: 380–389.

[68] Rosu T., Pahontu E., Mezey R.-S., Ilies D.-C., Georgescu R., Shova S., Gulea A., Synthesis, structural and spectral studies of Cu(II) and V(IV) complexes of a novel Schiff base derived from pyridoxal. Antimicrobial activity. Polyhedron. 2012; **31**: 352–360.

[69] Maki A.H., McGarvey B.R., Electron spin resonance in transition metal chelates. I. Copper(II) bis-acetylacetonate. Journal of Physical Chemistry. 1958; **29**: 31–34.