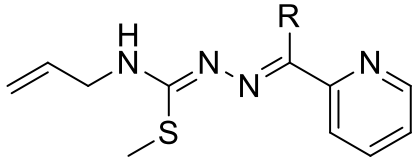
SOME 3D METAL COORDINATION COMPOUNDS WITH 2-FORMYLPYRIDINE 4-ALLYL-S-METHYLISOTHIOSEMICARBAZONE AND ITS DERIVATIVES: SYNTHESIS, CHARACTERIZATION, BIOLOGICAL ACTIVITY

Irina USATAIA, Vasilii GRAUR, Aurelian GULEA
CZU: 544.142.3
departamentchimie@mail.ru,
vgraur@gmail.com,
guleaaurelian@gmail.com

For many years, thiosemicarbazones have been of interest from the point of view of their biological activity, that depends on the structure of molecules and on the arrangement of functional groups. Isothiosemicarbazones are of biological interest since thioalkylation leads to a change in the coordination mode.

Therefore, the present paper describes the chemical synthesis, characterization and *in vitro* biological evaluation of 2-formylpyridine (**HL^{1}**), 2-acetylpyridine (**HL^{2}**), 2-benzoylpyridine (**HL^{3}**) 4-allyl-S-methylisothiosemicarbazones **(Scheme 1)** and its zinc(II), copper(II), nickel(II), cobalt(III) and iron(III) coordination compounds.



Scheme. Isothiosemicarbazone ligands **HL^{1}** (R=H), **HL^{2}** (R=CH_3), **HL^{3}** (R=C_6H_5)

The isothiosemicarbazone proligands were characterized by nuclear magnetic resonance (NMR) (^{1}H and ^{13}C), infrared spectroscopy (IR), and X-ray diffraction. All the coordination compounds were characterized by elemental analysis, IR, molar conductivity, and magnetic susceptibility measurements. 4-Allyl-S-methylisothioseimicarbazones (**HL$^{1-3}$**) were obtained similarly to the method described in the literature [1, 2].

New zinc(II), copper(II), nickel(II) and cobalt(III) complexes, $[Zn(HL^{1})_2]I_2$ **(1)**, $[Cu(HL^{1})Cl_2]$ **(2)**, $[Cu(HL^{1})Br_2]$ **(3)**, $[Cu(HL^{1})(H_2O)_2](ClO_4)_2$ **(4)**, $[Ni(HL^{1})_2]I_2{\cdot}H_2O$ **(5)**, $[Co(L^{1})_2]Cl$ **(6)**, $[Co(L^{1})_2]NO_3$ **(7)**, $[Co(L^{1})_2]I{\cdot}[Co(L^{1})_2](I_3)$ **(8)** were obtained with **HL^{1}** [3]. The complexes $[Zn(HL^{2})I_2]$ **(9)**, $[Cu(HL^{2})Cl_2]$ **(10)**, $[Cu(HL^{2})Br_2]$ **(11)**, $\{[Cu(HL^{2})NO_3]NO_3\}n$ **(12)**, $[Ni(HL^{2})_2](NO_3)_2$ **(13)**, $[Fe(L^{2})_2]NO3$ **(14)**, $[Co(L^{2})_2]NO_3$ **(15)**, and $[Co(L^{2})_2]Cl{\cdot}H_2O$ **(16)**, were obtained with **HL^{2}** [4]. Also were synthesized five new metal complexes $[Cu(HL^{3})Cl_2]$ (**17**), $[Cu(HL^{3})Br_2]{\cdot}H_2O$ (**18**), $[Cu(HL^{3})(NO_3)_2]{\cdot}2H_2O$ (**19**), $[Ni(HL^{3})_2]{\cdot}(NO_3)_2{\cdot}H_2O$ (**20**), $[Co(L^{3})_2]I$ (**21**) with **HL^{3}** pro-ligand [5].

Coordination compounds **(1–21)** were synthesized by interaction of $\mathbf{HL^{1-3}}$ and corresponding copper(II) salts in a 1:1 molar ratio or nickel(II), iron(III), and cobalt(II) salts in a 2:1 molar ratio. Zinc coordination compounds **(1), (9)** were obtained by interaction of zinc acetate dehydrate, $\mathbf{[H_2L^{1-2}]I}$, and potassium iodide in a 1:1:1 molar ratio. In reported coordination compounds, the isothiosemicarbazones coordinates to the metal atom in a tridentate manner using the NNN set of donor atoms in compounds **(1-8), (10), (12-16)**, but unusual for isothiosemicarbazones SNN mode of coordination in complexes $[Zn(HL^2)I_2]$ **(9)** and $[Cu(HL^2)Br_2]$ **(11)**. Such coordination mode of this type of ligands has been reported only for coordination compounds with palladium(II) [6]. The crystal structures of **(9)** and **(11)** demonstrate the first examples of SNN-coordination mode of isothiosemicarbazones to zinc(II) and copper(II) atoms.

The antiproliferative properties of these compounds towards human cervical epithelial HeLa, human epithelial pancreatic adenocarcinoma BxPC-3, human muscle rhabdomyosarcoma spindle, large multinucleated RD cancer cell lines, and normal kidney epithelial MDCK cell line have been investigated. The screening results showed that the synthesized substances inhibit proliferation of the studied cancer cells at concentrations 100–0.1 μ M. The substitution of 2-formylpyridine moiety with 2-acetylpyridine moiety in pro-ligand leads to a significant intensification of antiproliferative activity towards HeLa and BxPC-3 cells. In most cases, 3*d* metal coordination compounds are more active than isothiosemicarbazones. The series of copper coordination compounds can be used to trace the effect of the acid residue anion on the anticancer activity. The activity increases in the following order: $Cl^- < NO_3^- < Br^-$. The highest selectivity is achieved in the case of bromide ions. Cobalt complex $[Co(L^1)_2]Cl$ selectively inhibits proliferation of HeLa cells (SI > 47) and practically does not influence the growth of normal cells. Its SI value towards this cancer cell is more than 60 times higher than the corresponding SI value of doxorubicin that is used in medical practice.

Comparing the obtained results of antiproliferative activity for coordination compounds with $\mathbf{HL^1}$ and $\mathbf{HL^2}$, it can be concluded that the introduction of methyl radical into the azomethine group led to an increase of antiproliferative activity against cancer (HeLa, BxPC-3 and RD) and normal cells and also to an increase of the selectivity of the anticancer action. The study of the influence of synthesized compounds on healthy MDCK cells showed that in case of 2-formylpyridine 4-allyl-S-methylisothiosemicarbazone, complexes have lower cytotoxic effect on healthy cells of human organism. It makes these substances perspective for their use as anticancer drugs.

The results of the antimicrobial activity study showed that $\mathbf{HL^{1-3}}$ and its complexes manifest bacteriostatic and bactericidal properties. It has been observed, that the isothiosemicarbazones $\mathbf{HL^{1-3}}$ and studied coordination compounds manifest antimicrobial activities within the concentration limits 0.7–500 μ g/ml. The most

vulnerable to the studied substances was *S. aureus*. The comparison of the activity of **HL[1]** with the activity of **HL[2]** and **HL[3]** shows that the substitution of 2-formylpyridine moiety with 2-benzoylpyridine moiety leads to a significant intensification of antimicrobial activity especially towards Gram-negative bacteria's *K. pneumoniae*, *E. coli* and fungi *C. albicans*. The activities of isothiosemicarbazones decrease in the row **HL[3]** > **HL[1]** > **HL[2]**. The coordination of pro-ligands to copper(II) ions results in reduction of minimum inhibitory concentrations and minimum bactericide concentrations towards studied bacteria and fungi. The results show that copper complexes $[Cu(HL^2)Cl_2]$ **(10)**, $[Cu(HL^2)Br_2]$ **(11)** are the most active toward gram-negative bacteria *E. coli* (MIC/MBC = 7 ($\mu g \cdot ml^{-1}$)). The substitution of 2-formylpyridine moiety with 2-acetylpyridine moiety in copper(II) complexes leads to an intensification of antimicrobial activity especially towards Gram-negative bacteria and fungi. The studied coordination compounds also exceed the activity of furacillinum and nystatine against studied strains of microorganisms.

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