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SYNTHESIS, STRUCTURE AND BIOLOGICAL ACTIVITY OF N(4)-ALLYL-3-THIOSEMICARBAZONES AND THEIR COORDINATION COMPOUNDS WITH SOME 3D METALS

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The paper presents a review of different N(4)-allyl-3-thiosemicarbazones and their coordination compounds described in literature. N(4)-allyl-3-thiosemicarbazide can form corresponding thiosemicarbazones with aliphatic, aromatic and heteroaromatic carbonyl compounds. In the presence of transitional metal ions they can form coordination compounds of different structures. Both coordination compounds and proligands manifest antitumor, antibacterial, antiviral, and antimalarial activities. Copper(II) coordination compounds with these ligands manifest better antitumor activity than corresponding proligands.

Keywords: *N(4)-allyl-3-thiosemicarbazone, complexes, biological activity.*

SINTEZA, STRUCTURA ŞI ACTIVITATEA BIOLOGICĂ A N(4)-ALIL-3-TIOSEMICARBAZONELOR ŞI A COMPUŞILOR COORDINATIVI AI UNOR METALE 3D CU ACEŞTI LIGANZI

Lucrarea prezintă o revistă a N(4)-alil-3-tiosemicarbazonelor şi a compuşilor coordinativi cu aceşti liganzi descrise în literatura de specialitate. N(4)-alil-3-tiosemicarbazida formează tiosemicarbazone cu aldehide şi cetone alifatice, aromatice şi heteroaromatice. În prezenţa ionilor de metale de tranziţie acestea pot forma compuşi coordinativi cu diferite structuri. N(4)-alil-3-tiosemicarbazonele şi compuşii coordinativi manifestă activitate antitumorală, antibacterială, antivirală şi antimalarică. Compuşii coordinativi ai cuprului cu aceşti liganzi manifestă activitate antitumorală sporită în comparaţie cu N(4)-alil-3-tiosemicarbazonele corespunzătoare.

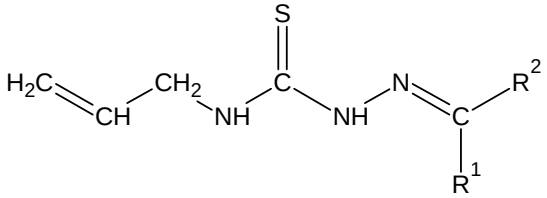
Cuvinte-cheie: *N(4)-alil-3-tiosemicarbazone, complecşi, activitate biologică.*

Introduction

Thiosemicarbazones is a class of organic compounds that possesses a wide spectrum of biological activities and medical properties.

Thiosemicarbazones contain a wide range of donor atoms and form with transition metal ions coordination compounds with various composition, structure, and properties [1]. Thiosemicarbazones and coordination compounds with them are of considerable interest because of their potentially beneficial biological activities, such as antitumor, antibacterial, antiviral, and antimalarial activities [2-4]. Thiosemicarbazides can be easily obtained from corresponding isothiocyanates. After that thiosemicarbazones are obtained by condensation reaction with different aldehydes or ketones [5].

Allylisothiocyanate is an organic compound which occurs naturally in food, e.g. in horseradish and mustard [6]. It is also used as a flavouring substance. For the proposed uses as a food additive, it is produced from seeds of brown mustard (*Brassica juncea*). It is used in food industry as a preservative that is added to the packaging of certain foods. It prevents food from spoilage. It is also used in medicine as a rubefacient (counterirritant), as a fumigant, in ointments, in mustard plasters, as an adjuvant, as a fungicide, as a repellent for cats and dogs and as a preservative in animal feed [7]. As allyisothiocyanate can be easily transformed into N(4)-allyl-3-thiosemicarbazide and N(4)-allyl-3-thiosemicarbazones afterwards it is of interest to collect and analyze the existing information in literature on this subject.



Scheme 1. N(4)-allyl-3-thiosemicarbazone proligand
R^1=H, CH_3, C_6H_5, C_5H_4N; R^2=C_6H_4OH, C_5H_4N

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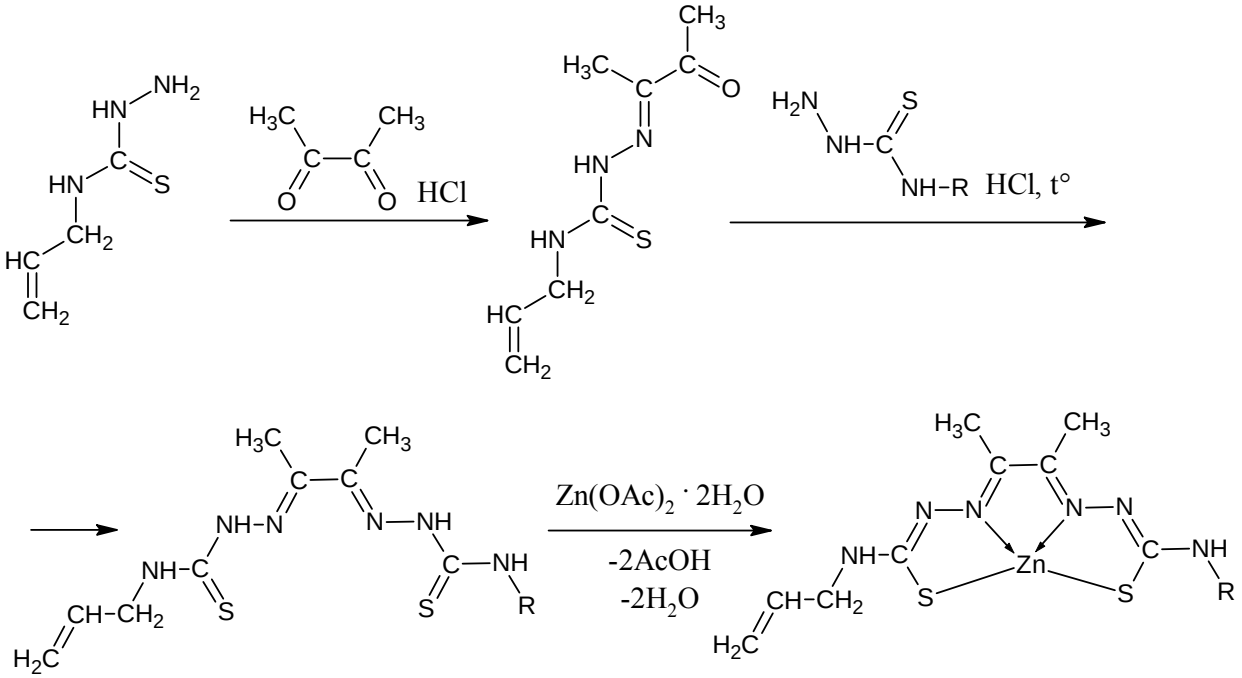
N(4)-allyl-3-thiosemicarbazones of aliphatic aldehydes and ketones and coordination compounds with them

N(4)-allyl-3-thiosemicarbazones of aliphatic aldehydes and ketones are relatively rarely found in literature. Diketones and dialdehydes are mainly used in such reactions that allows to obtain tetradentate bis(thiosemicarbazones) with symmetric structures [8]. The syntheses of glyoxal and butane-2,3-dione bis(N(4)-allyl-3-thiosemicarbazones) are described in [9]. These symmetric bis(N(4)-allyl-3-thiosemicarbazones) were obtained by the reaction between N(4)-allyl-3-thiosemicarbazide and corresponding dicarbonyl compound in 2:1 molar ratio in dioxane in case of glyoxal or water with catalytic amount of acetic acid in case of butane-2,3-dione. However the synthesis methods of two new types of unsymmetrical bis(thiosemicarbazone) proligands using 2,3-butandion as a carbonylic component are described in [10].

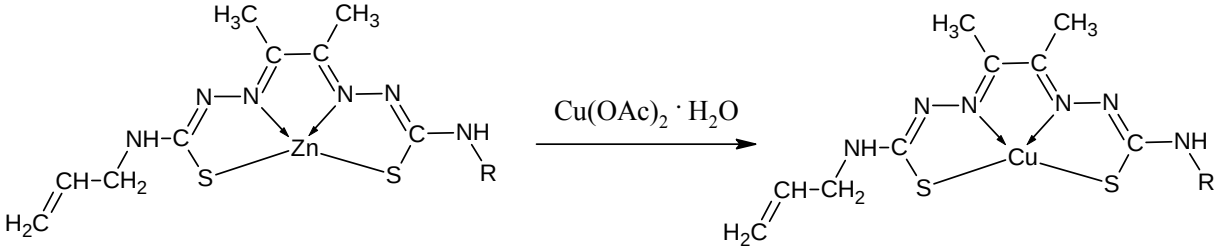


Scheme 2. Synthesis of unsymmetrical bis(thiosemicarbazone) and its zinc(II) coordination compound (R=H, CH_3, C_2H_5)

The key step in the synthesis of unsymmetrical bis(thiosemicarbazone) proligands is the isolation of the monoketothiosemicarbazone intermediate. For realizing this step 120% of the equivalent amount of butane-2,3-dione is rapidly added to the water solution of N(4)-allyl-3-thiosemicarbazide at 0^0C, that also contains a few drops of concentrated HCl as a catalyzer.

Excess of diketone prevents forming of symmetric bis(thiosemicarbazone). After that the resulting monoketothiosemicarbazone is purified by repeated recrystallization from ethanol. The purified product reacts in ethanol solution with another thiosemicarbazide or N(4)-substitutedthiosemicarbazide forming an asymmetric bis(thiosemicarbazone). If a non-substituted thiosemicarbazide was used at the second step of the reaction, then the terminal amino group can be functionalized with some monosaccharides.

The synthesis of zinc complexes was performed by reaction between zinc acetate and corresponding bis(thiosemicarbazones). The copper coordination compound can be obtained using transmetallation reaction.



Scheme 3. The transmetallation reaction (R=H, CH_3, C_2H_5)

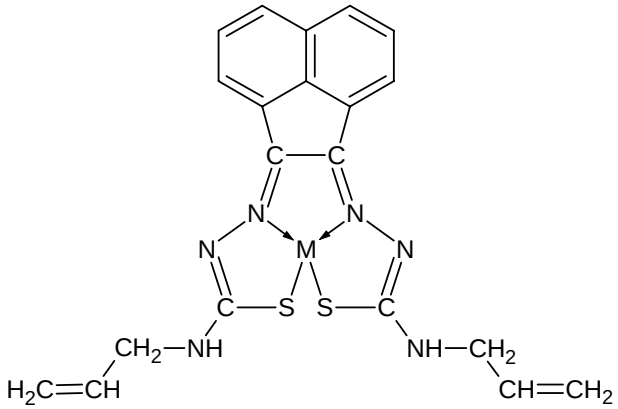
The zinc(II) with bis(thiosemicarbazone) ligands are fluorescent. Therefore fluorescent microscopy can be used to track the intracellular distribution of the complexes in different cells, including cancer cells, which is important for understanding the mechanism of the antitumor activity of these coordination compounds. Transmetallation allows radiolabeling coordination compound with ^{64}Cu isotope.

N(4)-allyl-3-thiosemicarbazones of aromatic aldehydes and ketones and their coordination compounds

The synthesis of several N(4)-allyl-3-thiosemicarbazones of mono- and dihydroxybenzaldehydes is described in [11]. These proligands are proposed as organic precipitating agents for Bi^{3+} and Cu^{2+} ions.

N(4)-allyl-3-thiosemicarbazones of salicylaldehyde and some of its derivatives are described in literature. The first description of salicylaldehyde N(4)-allyl-3-thiosemicarbazone can be found in [12]. The IR, ^{1}H and ^{13}C NMR spectra of salicylaldehyde and 3-methoxysalicylaldehyde N(4)-allyl-3-thiosemicarbazones are described in [13]. The synthesis of 5-bromosalicylaldehyde N(4)-allyl-3-thiosemicarbazone and it characteristics are specified in [14]. There are three signals in the ^{1}H NMR spectra of all these proligands that correspond to the hydrogen atoms of the allyl moiety: 5.65 (m, 1H, -CH=), 4.89 (d-d, 2H, $=CH_2$), 3.96 (d, 2H, N-CH_2-).

In [15] zinc and nickel coordination compounds with acenaphthenequinone bis(N(4)-allyl-3-thiosemicarbazone) were obtained using template synthesis in glacial acetic acid at 120^0C using four-fold excess of N(4)-allyl-3-thiosemicarbazide. The resultant zinc coordination compound was then transferred into copper coordination using transmetallation. This reaction allowed obtaining ^{64}Cu coordination compound that was subsequently used for detection of this radiolabeled species in breast cancer carcinoma cells.

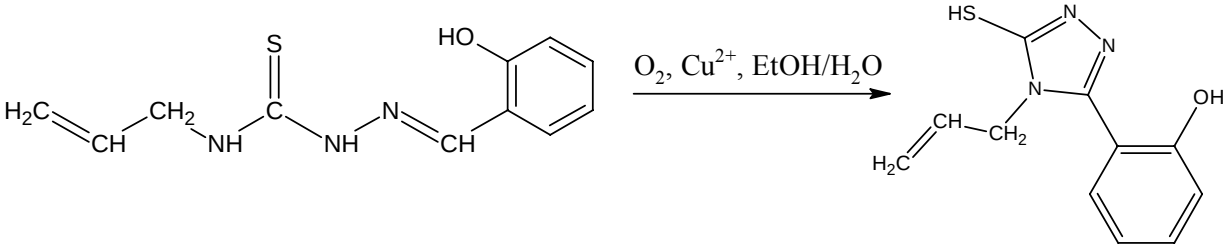


Scheme 4. The general structure of coordination compounds with acenaphthenequinone bis(N(4)-allyl-3-thiosemicarbazone) (M=Zn, Ni, Cu)

The diamagnetic zinc and nickel complexes were studied using NMR-, mass- and IR- spectroscopies. Their monocrystals were analyzed using X-ray diffraction. It was found that these coordination compounds are fluorescent. This property allowed to determine that these coordination compounds are well distributed within the cytoplasm of cancer cells but the nature of the localization was not established.

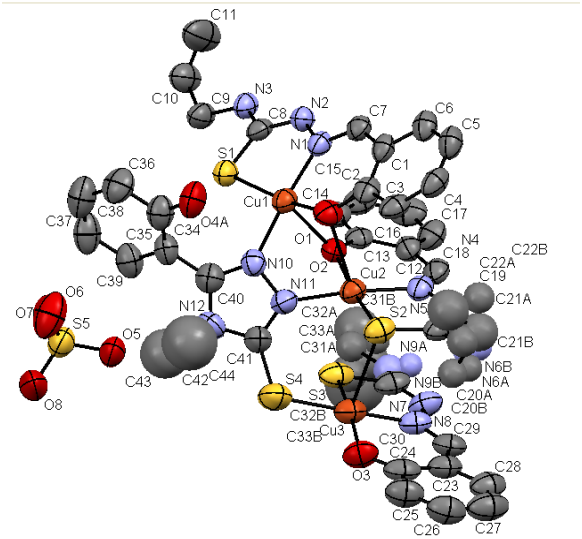
In 2011 the structure of trinuclear copper(II) compound was described in [16]. It was obtained by the reaction between copper (II) sulphate and salicylaldehyde N(4)-allyl-3-thiosemicarbazone. The composition of the coordination compound can be represented by the next formula $[Cu_3(C_{11}H_{12}N_3OS)_3(C_{11}H_{10}N_3OS)]SO_4 \cdot 3H_2O$.

It was detected that during keeping of the reaction mixture in aqueous ethanol solution at room temperature an oxidative cyclization of the starting thiosemicarbazone takes place (scheme 5).



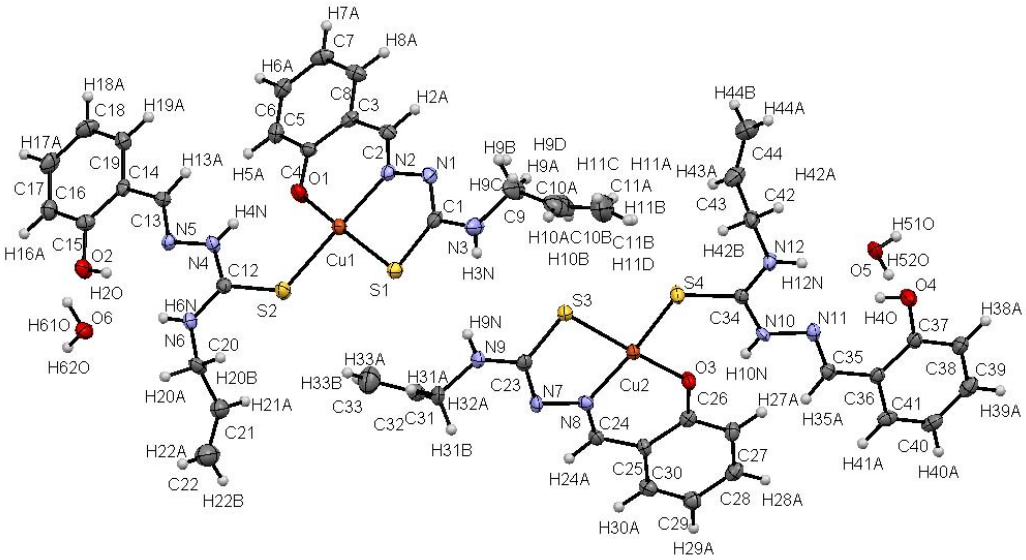
Scheme 5. Oxidative cyclization of salicylaldehyde N(4)-allyl-3-thiosemicarbazone

The resultant triazol coordinates to three different copper atoms with different donor atoms forming trinuclear coordination compound. Other three salicylaldehyde N(4)-allyl-3-thiosemicarbazone molecules also coordinated to each of the three copper atoms. The structure of the complex consists of three square fragments. Three coordination positions are occupied by starting proligand. The forth coordination positions are occupied by triazole nitrogen atom or thiol sulphur atom.



Scheme 6. The structure of $[Cu_3(C_{11}H_{12}N_3OS)_3(C_{11}H_{10}N_3OS)]SO_4 \cdot 3H_2O$

In 2010 [17] it was described the first structure of square-planar copper(II) coordination compound with two salicylaldehyde N(4)-allyl-3-thiosemicarbazone ligands that coordinate in different way to the central atom (scheme 7). One molecule of thiosemicarbazone coordinates as a tridentate ONS-ligand. The other molecule of thiosemicarbazone acts like a monodentate ligand using only its sulphur atom. The complex is stabilized by an intramolecular hydrogen bond, which forms a six-membered pseudo-chelate metallacycle. Tridentate ligand is in the E-isomeric form. Monodentate ligand is in the Z-isomeric form.

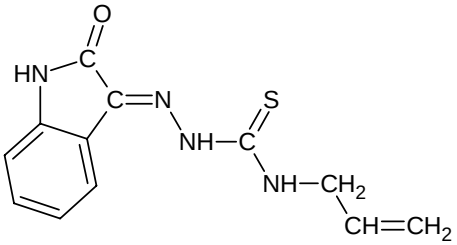


Scheme 7. The structure of $[Cu(C_{11}H_{11}N_3OS)(C_{11}H_{13}N_3OS)]\cdot H_2O$

The synthesis of this coordination compound was performed using the reaction between aqueous solution of copper(II) acetate and ethanolic solution of salicylaldehyde N(4)-allyl-3-thiosemicarbazone taken in 1:2 molar ratio. In the course of slow evaporation at room temperature violet single-crystals were obtained.

N(4)-allyl-3-thiosemicarbazones of heteroaromatic aldehydes and ketones and their coordination compounds

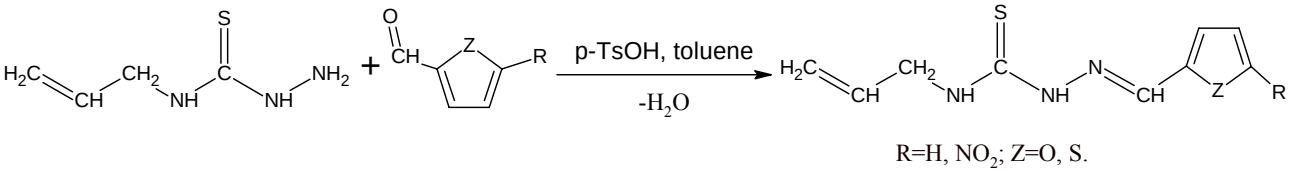
In [18] different isatin N(4)-substituted-3-thiosemicarbazones have been studied. The isatin N(4)-allyl-3-thiosemicarbazone was synthesized in ethanolic solutions by reaction between isatin and N(4)-allyl-3-thiosemicarbazide in the presence of catalytic amounts of acetic acid.



Scheme 8. Isatin N(4)-allyl-3-thiosemicarbazone

The anticancer activity of these substances was tested on adenocarcinoma, breast cancer, and colorectal cancer cells. The obtained results show that they posses anticancer activity (IC_{50} values are 1-37μM), but the selectivity of their action is low.

Various substituted furan-2-carbadehyde and thiophene-2-carbaldehyde N(4)-ally-3-thiosemicarbazones [19] have been synthesized according to the following scheme:



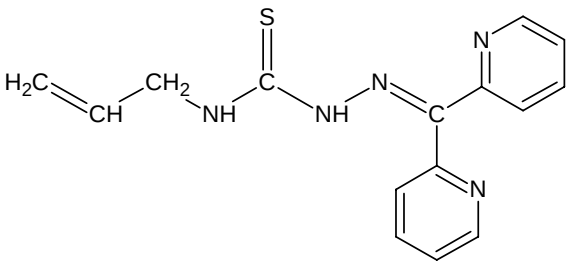
Scheme 9. The synthesis of thiophene and furan derivatives

The synthesis was executed at room temperature in toluene by the reaction between N(4)-ally-3-thiosemicarbazide and corresponding aldehyde in presence of catalytic amount of p-toluenesulfonic acid. The termination of the reaction was determinated by disappearance of aldehyde in the reaction mixture. The obtained solid compounds were filtered out and washed with small amounts of hexane. There structures were proved using IR, mass and NMR spectroscopies.

The 5-nitrofuran-2-carbadehyde and 5-nitrothiophene-2-carbaldehyde N(4)-ally-3-thiosemicarbazones were found to be the most active against *Trypanosoma cruzi* that causes Chagas disease (IC_{50} = 1.9 and 6,4μM, correspondingly). It was determined that presence of nitro group in these substances is crucial for the accumulation of squalene that is a precursor for biosynthesis of steroids. It was shown that synthesized substances don't show high antifungal activity. The minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) are modest and are over 250 μg/mL.

The α-(N)-heterocyclic thiosemicarbazones are formed by condensation reaction of thiosemicarbazides with corresponding heterocyclic aldehyde or ketones. These substances represent NNS tridentate ligands and possess high biological activity in many cases [20, 21].

Synthesis methods and properties of di-2-pyridylketone N(4)-ally-3-thiosemicarbazone and its iron complexes are described in [22].



Scheme 10. Structural formula of di-2-pyridylketone N(4)-ally-3-thiosemicarbazone (HDp4aT)

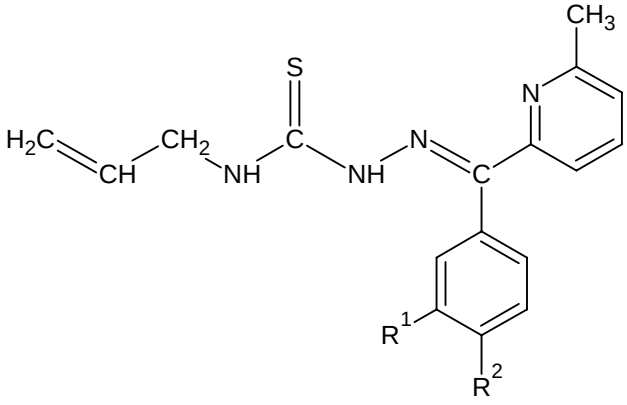
It was shown that synthesized proligands possess selective antitumor activity against SK-N-MC neuroepithelioma cells. The experiment showed that unsubstituted thiosemicarbazone posseses the lowest activity (IC_{50}=5.20μM), while substituted 4,4-dimethyl-, 4-phenyl, 4-allyl, 4-ethyl thiosemicarbazones possess similar activity (IC_{50}=0,01-0,05μM). The formation of Fe(II) and Fe(III) coordination compounds leads to the decrease of antitumor activity in 6-42 times. There is no significant difference between the activity of Fe(II) and Fe(III) coordination compounds. The authors of this paper presuppose that the decrease of activity is caused by the decrease of their ability to penetrate through cell membrane. The composition of synthesized coordination compounds can be presented by the next formulas: $[Fe(Dp4aT)_2]\cdot nH_2O$ and $[Fe(Dp4aT)_2](ClO_4)\cdot nH_2O$. Octahedral mer structures are presupposed for them.

Throughout this work it were obtained coordination compounds of copper(II), manganese(II), zinc(II), and nickel(II) with these ligands [23]. The obtained coordination compounds manifested the same antitumor activity as corresponding thiosemicarbazones. On this base it was presupposed that coordination compounds only serve the purpose of transportation of the ligands into the cells where the ligands are eliminated from the inner sphere in the process of dissociation.

A series of 2-benzoylpyridine and 2-(3-nitrobenzoyl)pyridine N(4)-substituted thiosemicarbazone among them N(4)-allyl-3-thiosemicarbazones and their iron complexes were described in [24]. It was found that these substances possess selective antitumor activity against SK-N-MC neuroepithelioma cells. It was showed up that there is a correlation between redox potentials and antitumor activity. The decrease of redox potential of iron coordination compounds leads to the growth of antitumor activity. Besides SK-N-MC cells it was studied the activity of synthesized compounds towards MRC-5 fibroblasts. The IC_{50} value for 2-benzoylpyridine N(4)-allyl-3-thiosemicarbazone is more than 6,25μM in case of fibroblasts and is equal to 0,004 μM in case of neuroepithelioma cells. These values for 2-(3-nitrobenzoyl)pyridine N(4)-allyl-3-thiosemicarbazone are 2,39 μM and 0,013 μM, correspondingly. Thereby, these substances selectively inhibit proliferation of SK-N-MC neuroepithelioma cells and the activity of 2-benzoylpyridine N(4)-allyl-3-thiosemicarbazone is higher. The introduction of electron-seeking substituent leads to the growth of redox potential and reduces the antitumor activity and selectivity of this action.

In 2011 [25] it was found that coordination compounds with di-2-pyridylketone and 2-benzoylpyridine N(4)-substituted thiosemicarbazones, previously described, inhibit HIV-1 transcription. The most active and the least toxic were N(4)-allyl- and N(4)-ethyl-3-thiosemicarbazones. The IC_{50} value for 2-benzoylpyridine N(4)-allyl- and N(4)-ethyl-3-thiosemicarbazone was found to be 0.13μM. The authors [26] presupposed that activity of these substances is interconnected with the stability of coordination compounds that are formed with iron ions.

In the article [27] the authors continued the study of substituted 2-benzoylpyridine N(4)-substituted thiosemicarbazones. Electron-donating substituents (methyl, methoxy) were introduced into 2-benzoylpyridine moiety (scheme 11).

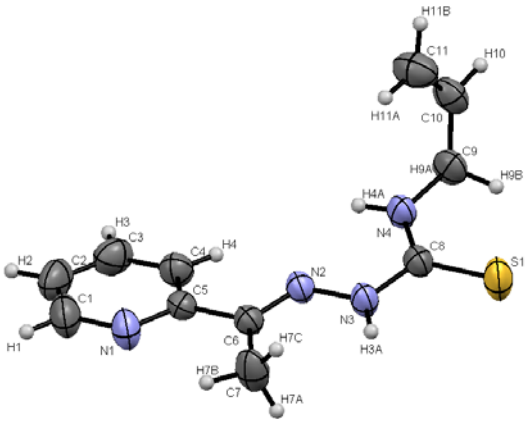


Scheme 11. Structural formula of substituted 2-benzoylpyridine N(4)-ally-3-thiosemicarbazone (R^1, R^2=H,OCH_3)

In was found that introduction of methoxy groups leads to growth of stability of iron coordination compound and redox potentials and reduces the antitumor activity.

Coordination compounds of substituted 2-benzoylpyridine thiosemicarbazone were described in the article [28]. The halogen atoms were introduced into the benzene fragment. The introduction of halogens resulted in a significant growth of antitumor activity. The authors link this growth of activity to the growth of lipophilic properties of this proligands. The activity grows in following sequence F<Cl<Br<I.

The synthesis and structure of 2-acetylpyridine N(4)-allyl-3-thiosemicarbazone were described in 2009 [29]. Its structure was determined using X-ray diffraction analysis (scheme 12).



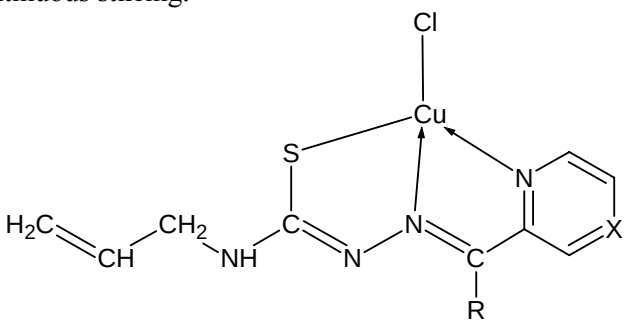
Scheme 12. The structure of 2-acetylpyridine N(4)-allyl-3-thiosemicarbazone

The majority of studied 2-acetylpyridine N(4)-substituted-3-thiosemicarbazone in this article possess high selective antitumor activity against SK-N-MC cells (IC_{50}=0.001-0.011μM). As in previous works, the authors of this work found the correlation between redox potentials of iron complexes and their antitumor activity. The lowest values of redox potentials and the highest antitumor activity of the substances of this type confirm the advanced hypothesis. The activity of iron coordination compounds is significantly lower than of the corresponding proligands. In most cases the activity of iron(II) and iron(III) coordination compounds differs slightly. But in case of iron complexes with 2-acetylpyridine N(4)-allyl-3-thiosemicarbazone the IC_{50} value for iron(II) coordination compound is 6 times lower than for iron(III) complex.

In [5] more than 173 thiosemicarbazides, semicarbazones, thiosemicarbazones including N(4)-allyl-derivatives are described. The synthesized thiosemicarbazones manifest antimalarial properties. The corresponding semicarbazones don't possess this activity. On this basis it was determined the necessity of thiocarbonyl group in the molecule's structure for antimalarial activity.

In US patents [30,31] the synthesized 2-acetyl- and 2-propionylpyridine thiosemicarbazones were proposed for treatment malaria, gonorrhea, bacterial infections.

The antitumor activity of α-(N)-heterocyclic-N(4)-substituted thiosemicarbazones in comparison with their copper(II) complexes was reported in 2011 [32]. The synthesis of copper(II) coordination compounds was realized by heating the ethanolic solutions of equimolar amounts of copper(II) chloride and corresponding thiosemicarbazone with continuous stirring.



Scheme 13. The general structural formulf of synthesized cooper(II) coordination compounds.

The copper(II) coordination compounds manifest higher antitumor activity towards SK-BR-3 and MCF-7 breast cancer cells than corresponding thiosemicarbazones.

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Table 1

The IC_{50} values for SK-BR-3 and MCF-7 breast cancer cells

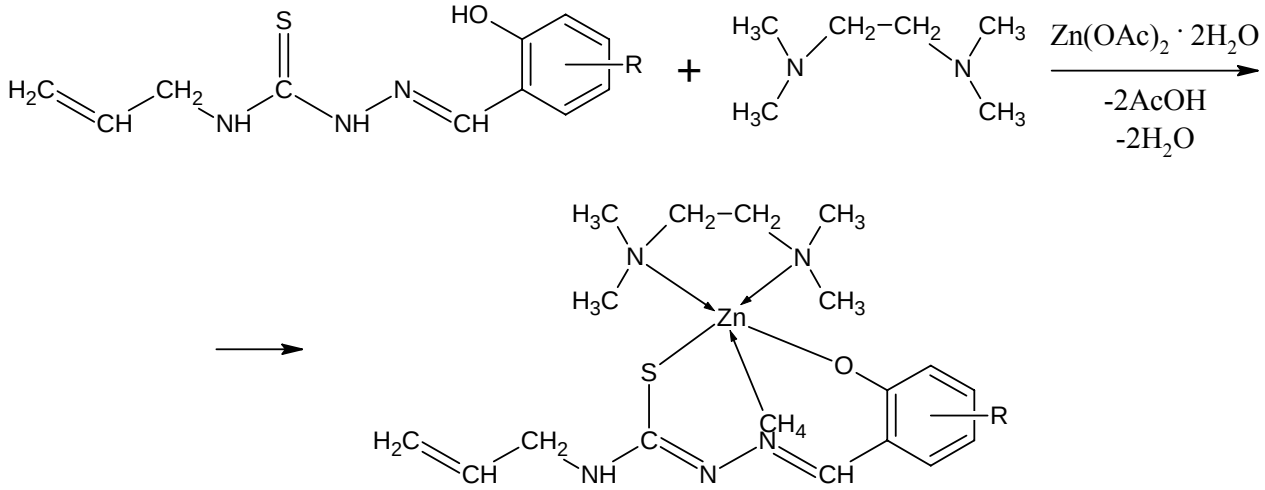
	IC_{50}, μM SK-BR-3	IC_{50}, μM MCF-7
HFp4alT (2-formylpyridine N(4)-allyl-3-thiosemicarbazone)	8.1±1.0	-
Cu(Fp4alT)Cl	0.8±03	4.6±0.5
HAp4alT (2-acetylpyridine N(4)-allyl-3-thiosemicarbazone)	6.1±0.8	-
Cu(Ap4alT)Cl	1.3±0.4	2.5±0.2

Mixed-ligand coordination compounds with some amines and phosphines.

Alongside with thiosemicarbazones the molecules of amines and phosphines can be placed in the inner sphere of these complexes [33-37]. In many cases the introduction of amines has an influence on the biological activity of these complexes [2].

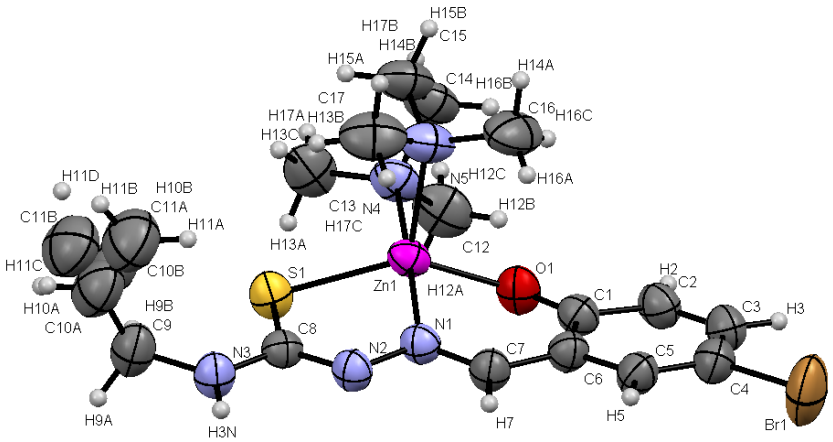
In literature are described the syntheses of a number of zinc and cobalt coordination compounds with salicylaldehyde, 5-bromo- and 3-methoxysalicylaldehyde N(4)-allyl-3-thiosemicarbazones and N,N,N',N'-tetramethylethylenediamine (tmen) [13, 38].

The general scheme of zinc coordination compound synthesis can be represented in the following way (scheme 14):



Scheme 14. The formation of the [Zn(L)tmen] complexes

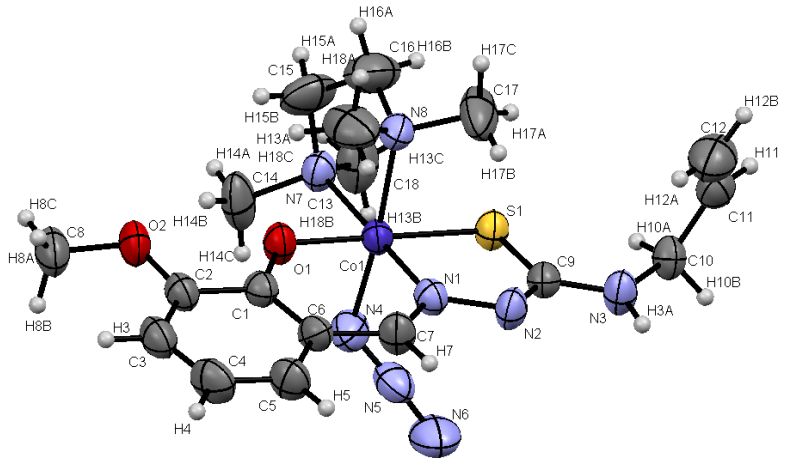
The composition and structures of these complexes were studied using elemental analysis, molar conductivity, IR and NMR spectroscopy and X-ray diffraction analysis. The structure of zinc coordination compound with 5-bromo- and 3-methoxysalicylaldehyde N(4)-allyl-3-thiosemicarbazone is shown in scheme 15.



Scheme 15. The structure of [Zn(L)tmen] complex.

The complex has a square pyramidal structure. The thiosemicarbazone acts as a tridentate ligand and coordinates to the central atom by phenolic oxygen atom, thiolato sulphur atom, and azomethinic nitrogen atom. The remained two positions in the inner sphere are occupied by nitrogen atoms of N,N,N',N'-tetramethylethylenediamine. The deprotonation of the ligand was proved by NMR spectroscopy. The peaks of hydrogens from OH and NH groups are absent in the ^{1}H NMR spectra, that can be found in ^{1}H NMR spectra of the corresponding thiosemicarbazone at 11,19ppm and 10,30ppm. The coordination of the azomethinic nitrogen atom to the central atoms leads to displacement of the hydrogen peak of the azomethnic group by 0.2ppm.

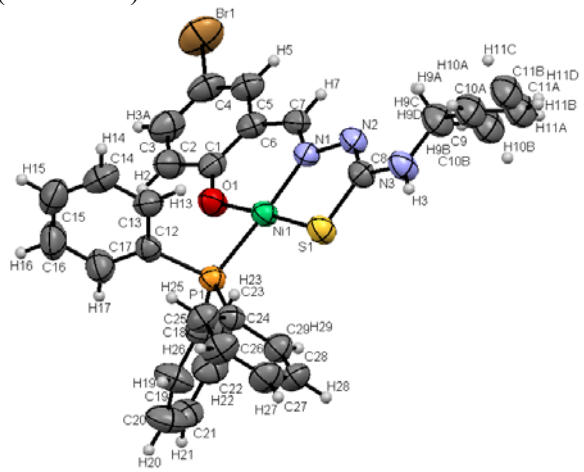
The coordination compounds of cobalt [13] were synthesized by the reaction between cobalt(II) acetate, corresponding N(4)-allyl-3-thiosemicarbazone, N,N,N',N'-tetramethylethylenediamine and sodium azide taken in molar ratio 1:1:1:1.5. Cobalt(II) is oxidized by oxygen from air up to cobalt(III). The X-ray diffraction analysis for one of the synthesized coordination compounds showed that one molecule of corresponding N(4)-allyl-3-thiosemicarbazone, one molecule of N,N,N',N'-tetramethylethylenediamine, and one azide-ion are coordinating to the central atom. The N(4)-allyl-3-thiosemicarbazone acts like a doubly deprotonated tridentate ONS-ligand. Its crystal structure has a slightly distorted octahedral coordination geometry (scheme 16).



Scheme 16. The structure of [CoL(tmen)(N_3)]

Antimicrobial, antifungal, antitumor and other biological properties of these mixed-ligand coordination compounds were not studied.

It is described a method of nickel coordination compounds with salicylaldehyde and 5-bromosalicylaldehyde N(4)-allyl-3-thiosemicarbazones [14]. As a source of nickel it was used dichlorobis(triphenylphosphine)nickel. The initial substances were taken in 1:1 molar ratio. Dichloromethane and absolute ethanol were used as solvents. The reactions were held in nitrogen atmosphere. As a result red square-planar coordination compounds were obtained. Thiosemicarbazone acts as a doubly deprotonated ONS-ligand. The fourth coordination position is occupied by a triphenylphosphine molecule. The structure of one coordination compound was demonstrated by X-ray diffraction analysis (scheme 17).



Scheme 17. The structure of [NiL(PPh_3)]

Conclusions

N(4)-allyl-3-thiosemicarbazones of aliphatic, aromatic and heteroaromatic aldehydes and ketones and their coordination compounds with zinc, copper, iron and cobalt are represented in this review. Thiosemicarbazones coordinate to the 3d metal ions by sulphur atom, azomethinic nitrogen atom and also can coordinate by other donor atom of carbonyl moiety if a five- or six-membered metallacycle is formed. So the N(4)-allyl-3-thiosemicarbazones can be at least bidentate. Though, it was found that they can also act like monodentate ligands coordinating only by sulphur atom. These proligands and coordination compounds with them manifest antitumor, antibacterial, antiviral, and antimalarial activities. Proligands, containing aliphatic carbonyl moiety, possess weaker biological activity. The most active proligands contain heteroaromatic carbonyl moiety. Coordination with iron usually leads to a decrease of biological activity. Copper(II) coordination compounds with these ligands manifest better antitumor activity than corresponding proligands.

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