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BIOLOGICALLY ACTIVE COORDINATION COMPOUNDS BASED ON 4-ALLYLTHIOSEMICARBAZONES AND THEIR DERIVATIVES: SYNTHESIS, STRUCTURE, AND PROPERTIES

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Abstract

This report presents the synthesis, structural characterization, and biological evaluation of 4-allylthiosemicarbazide derivatives, including thiosemicarbazones, isothiosemicarbazones, and their transition metal complexes (Zn(II), Cu(II), Ni(II), Co(III), and Fe(III)). The ligands were obtained from 4-allylthiosemicarbazide, a derivative of allyl isothiocyanate. The resulting coordination compounds show diverse structures, including mono-, bi-, and polynuclear systems with square-planar, pyramidal, and octahedral geometries. Biological studies revealed significant antiproliferative, antibacterial, antifungal, and antiradical activities. Cu(II) complexes exhibit the highest antibacterial and antiproliferative effects, while Ni(II), Fe(III), and Co(III) complexes demonstrate improved selectivity toward cancer cells. Structural modifications and metal ion choice strongly influence biological activity.

Keywords: 4-allylthiosemicarbazide, 4-allylthiosemicarbazones, *S*-substituted 4-allylisothiosemicarbazones, antiproliferative activity, antibacterial activity, antiradical activity.

COMPUȘI COORDINATIVI BIOLOGIC ACTIVI PE BAZĂ DE 4-ALILTIOSEMICARBAZONE ȘI DERIVAȚII ACESTORA: SINTEZĂ, STRUCTURĂ ȘI PROPRIETĂȚI

Rezumat

Acest raport prezintă sinteza, caracterizarea structurală și evaluarea biologică a derivaților 4-aliltiosemicarbazidei, inclusiv tiosemicarbazone, izotiosemicarbazone și complecșii lor cu metale de tranziție (Zn(II), Cu(II), Ni(II), Co(III) și Fe(III)). Liganzii au fost obținuți din 4-aliltiosemicarbazidă, un derivat al izotiocianatului de alil. Compușii coordinativi obținuți prezintă o diversitate structurală, incluzând sisteme mono-, bi- și polinucleare, cu geometrii plan-pătrate, piramidale și octaedrice. Studiile biologice au evidențiat activitate antiproliferativă, antibacteriană, antifungică și antiradicalică semnificativă. Complecșii de Cu(II) prezintă cea mai ridicată activitate antibacteriană și antiproliferativă, în timp ce complecșii de Ni(II), Fe(III) și Co(III) demonstrează o selectivitate îmbunătățită față de celulele canceroase. Modificările structurale și natura ionului metalic influențează puternic activitatea biologică.

Cuvinte-cheie: 4-aliltiosemicarbazidă, 4-aliltiosemicarbazone, 4-alilizotiosemicarbazone *S*-substituite, activitatea antiproliferativă, activitatea antibacteriană, activitatea antiradicalică.

Introduction

Thiosemicarbazides, thiosemicarbazones, and their derivatives, as well as coordination compounds with this type of ligands attract a continuous interest of the scientists for their potential use as analytical reagents and biological properties [1]. As it was shown in many research articles, the substituents in the thiosemicarbazide moiety have a huge influence on the properties of the resultant thiosemicarbazide, its derivatives, and corresponding coordination compounds [2]. 4-Allylthiosemicarbazide and its derivatives are selected as the theme of this report.

4-Allylthiosemicarbazide (Figure 1) is a derivative of a natural product allyl isothiocyanate (Figure 2) [3]. This compound can be readily converted into 4-allylthiosemicarbazide and, upon condensation, into various thiosemicarbazones.

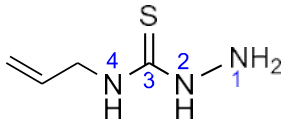


Figure 1. Structural formula of HL1 and atom numbering in thiosemicarbazide fragment.

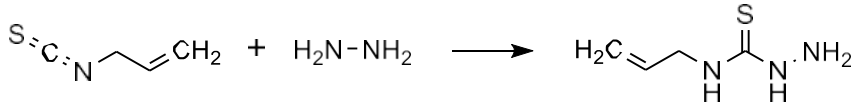


Figure 2. Reaction of 4-allylthiosemicarbazide formation form allyl isothiocyanate.

Materials and methods

The general scheme for the synthesis of 4-allylthiosemicarbazones is presented in Figure 3.

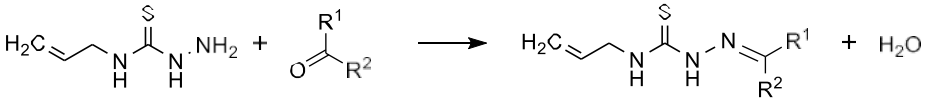


Figure 3. Synthesis of thiosemicarbazones

In the case of some ketones, a two-step reaction was employed (Figure 4) [4].

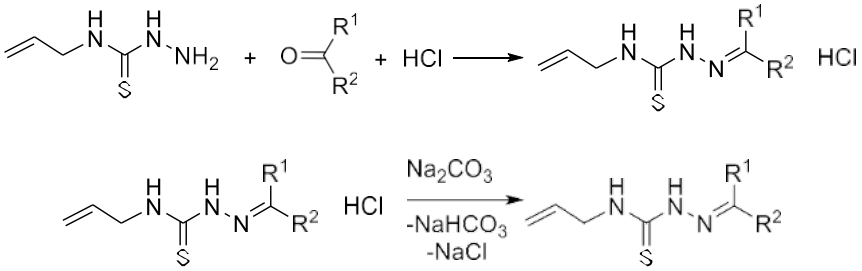


Figure 4. Two-step synthesis of thiosemicarbazones

The general scheme for the synthesis of *S*-substituted isothiosemicarbazones is presented in Figure 5.

Key findings and conclusions

A series of 4-allylthiosemicarbazide derivatives, including thiosemicarbazones and isothiosemicarbazones as well as their coordination compounds with transition metals (Zn(II), Cu(II), Ni(II), Co(III), and Fe(III)) were synthesized and structurally characterized [6-12]. The obtained complexes display a wide structural diversity, ranging from mono- and binuclear to polynuclear systems, with square-planar, pyramidal and octahedral coordination geometries.

The studied compounds exhibit pronounced biological activity, including antiproliferative, antibacterial, antifungal, and antiradical effects. Cu(II) complexes generally show the highest antiproliferative and antibacterial activity, although their selectivity toward cancer cells is moderate. In contrast, some Ni(II), Fe(III), and Co(III) complexes demonstrate improved selectivity, despite slightly lower overall cytotoxicity.

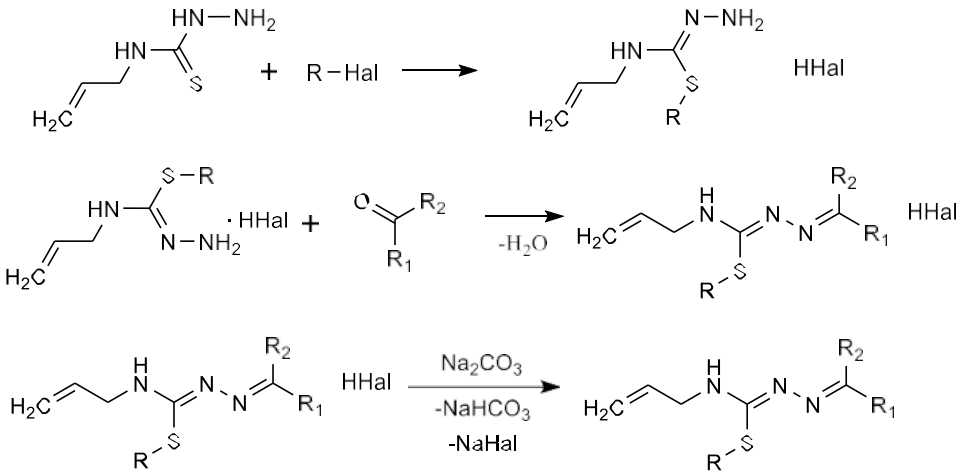


Figure 5. Synthesis of *S*-substituted isothiosemicarbazones [5]

Among the investigated systems, Cu(II) complexes with 4-allylthiosemicarbazones of 2-formylpyridine derivatives show the most promising antibacterial activity against both Gram-positive and Gram-negative bacteria. Modification of the coordination sphere, including the introduction of *N*-heteroaromatic co-ligands, significantly influences biological properties.

The transformation of thiosemicarbazones into *S*-substituted isothiosemicarbazones can enhance antifungal activity, indicating an important direction for structural modification. Additionally, both ligands and their metal complexes demonstrate notable antiradical properties, with Ni(II) complexes often showing higher activity than their Cu(II) analogues.

Overall, the results confirm that both metal ion nature and ligand modification play a crucial role in tuning biological activity and selectivity, making these systems promising candidates for the development of new antimicrobial, anticancer, and antioxidant agents.

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