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Evaluation of Anticancer Activity of Pyruvamide 4-Allylthiosemicarbazones and Their Copper(II) Complexes Against the Leukemia THP-1 Cell Line

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INTRODUCTION & AIM

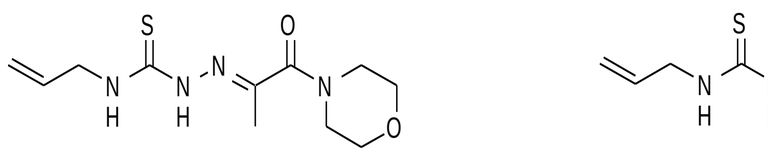
According to recent data from the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), cancer remains one of the leading public health challenges worldwide. Projections suggest that, due to demographic factors such as population growth and aging, the annual number of new cases could reach around 35 million by 2050. The WHO report also highlights that while progress has been made in prevention and treatment, access to effective diagnostic and therapeutic options remains uneven across different regions, particularly in low- and middle-income countries. Among hematological malignancies, leukemia represents a significant cause of cancer-related morbidity and mortality, and the THP-1 cell line, derived from human acute monocytic leukemia, is frequently used as an established *in vitro* model to evaluate the anticancer potential of new compounds. Thiosemicarbazones and their metal complexes are compounds that have long been recognized in the literature as biological agents, including those with anticancer properties. The aim of this work is the study of antiancer activity of pyruvamide 4-allylthiosemicarbazones and their copper(II) complexes against the leukemia THP-1 cell line.

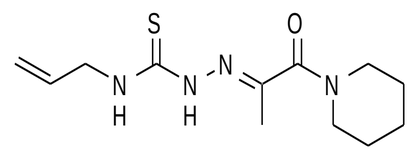
METHOD

Based on the above, for our study we synthesized a series of 4-allylthiosemicarbazones of various pyruvic acid amides (Figure 1): 1-(piperidin-1-yl)propane-1,2-dione 4-allylthiosemicarbazone (HL^1), 3-(morpholin-4-yl)propane-2,3-dione 4-allylthiosemicarbazone (HL^2), and *N*-(4-methoxyphenyl)-2-oxopropanamide 4-allylthiosemicarbazone (HL^3), along with their copper(II) chloride complexes [Cu(L^{1-3})Cl]. The physicochemical properties of all synthesized compounds were investigated to confirm their structure and composition using such method as ^1H and ^{13}C NMR spectroscopy, FTIR spectroscopy, X-ray diffraction analysis, elemental analysis and molar conductivity evaluation. The anticancer activity of the synthesized compounds was evaluated against the THP-1 cell line (human monocytic leukemia cell line). Determination of the number of viable cells after cultivation in the presence of various concentrations of the studied substances was carried out by the MTS assay. The 10-mM stock solutions of the studied compounds were prepared by dissolving 10 µmol of the corresponding compound in 1 mL of DMSO. The 0.1, 1, and 10 µM solutions were prepared by dilution of the stock solutions with the corresponding medium and used for the study of antiproliferative activity.

RESULTS & DISCUSSION

All copper(II) complexes exhibited higher activity than the corresponding thiosemicarbazones from which they were obtained. HL^1 and HL^3 showed no activity, while only 3-(morpholin-4-yl)propane-2,3-dione 4-allylthiosemicarbazone demonstrated activity with an IC_{50} value of 2.8 µM (Table 1). The most active compound was [Cu(L^2)Cl], with an activity value of 0.14 µM, which is 2.2 times higher than that of Doxorubicin, used as a reference standard in this study.





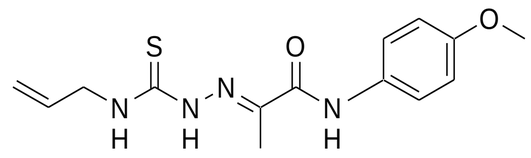


Figure 1. The structural formula of HL^{1-3}

Table 1. Anticancer activities of HL^{1-3} and their copper(II) complexes

Compound	IC_{50}, µM
HL^1	>10
[Cu(L^1)Cl]	0.95±0.02
HL^2	2.8±0.3
[Cu(L^2)Cl]	0.14±0.008
HL^3	>10
[Cu(L^3)Cl]	5.6±1.5
DOXO	0.32±0.06

CONCLUSION

The results obtained in this work provide deeper insight into the relationship between anticancer activity and structure, using 4-allylthiosemicarbazones and their copper(II) complexes as examples. A clear influence of the amide fragment on the activity of the thiosemicarbazone molecule is observed, as well as the fact that all synthesized copper(II) complexes are more active than their corresponding ligands. This indicates that ligand coordination to the copper(II) atom and its deprotonation can have a significant impact on the anticancer activity of the such type of compounds.

ACKNOWLEDGEMENT

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