Novel copper(II) complexes with S-substituted isothiosemicarbazone as high selective anticancer compounds against BxPC-3 cell line.

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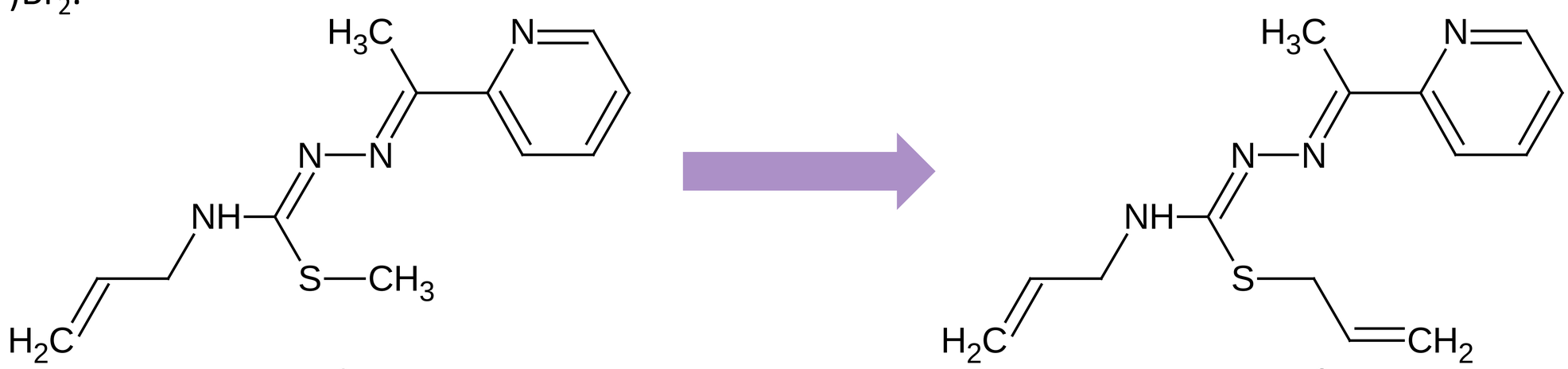
Introduction

Cancer is a major disease worldwide. Therefore, scientists are in constant search for new, more effective and selective, not damaging normal cells, substances for the treatment of this disease. The use of coordination compounds as such anticancer agents is based on the interaction between DNA and metal-based complexes. It is known that thiosemicarbazones, isothiosemicarbazones, and 3*d* metal complexes with them often exhibit high anticancer activity.

Object of study:

In this work S-methyl group in the composition of 2-acetylpyridine 4-allyl-S-methylisothiosemicarbazone[1] (HL^1) was replaced by an S-allyl group. So, the 2-acetylpyridine 4,S-diallylisothiosemicarbazone (HL^2) was obtained. Two novel copper(II) coordination compounds were synthesized with HL^2: $Cu(HL^2)Cl_2$ and $Cu(HL^2)Br_2$.



HL^1 **HL^2**

Compound	MDCK	BxPC-3	
	IC_{50}, μM	IC_{50}, μM	SI*
Doxorubicin	7,1	3,7	1,92
$[Cu(HL^1)Cl_2]$	1,00	0,09	**20**
$[Cu(HL^1)Br_2]$	0,35	0,02	**12**

Compound	MDCK	BxPC-3	
	IC_{50}, μM	IC_{50}, μM	SI*
Doxorubicin	7,1	3,7	1,92
$[Cu(HL^2)Cl_2]$	1,4	0,005	**280**
$[Cu(HL^2)Br_2]$	1,2	0,008	**154**

* SI = IC_{50}(MDCK) / IC_{50}(BxPC-3) – selectivity index

Results:

The inhibitory activity of these novel coordination compounds was tested and compared with the corresponding activities of previously described complexes with 2-acetylpyridine 4-allyl-*S*-methylisothiosemicarbazone. The inhibitory activity toward normal MDCK cell line has decreased. Their IC_{50} values are in the range of 1.2-1.4 μM, while the corresponding complexes with HL^1 have IC_{50} values 0.35-1.0 μM. So the novel complexes have a lower impact on normal cells. At the same time, the inhibitory activity toward human pancreatic cancer cell line (BxPC-3) has increased 2.5-18 times. The IC_{50} values of the novel complexes toward BxPC-3 cells are in the range of 5-8 μM. That means that the selectivity indexes (ratio between IC_{50} values towards normal cells and cancer cells) of the novel complexes are in the range of 150-280 which is very promising for further study of these complexes as potent selective anticancer drugs.

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References: 1. Graur, V., Usataia, I., Bourosh, P., Kravtsov, V., Garbuz, O., Hureau, C., Gulea, A. Synthesis, characterization, and biological activity of novel 3d metal coordination compounds with 2-acetylpyridine N^4-allyl-S-methylisothiosemicarbazone // Applied Organometallic Chemistry, 2021, Vol. 35, No. 4, p. e6172; DOI: 10.1002/aoc.6172

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