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Novel perspective of anticancer metal-based drugs: Characteristics of heterometallic complexes and their potential applications

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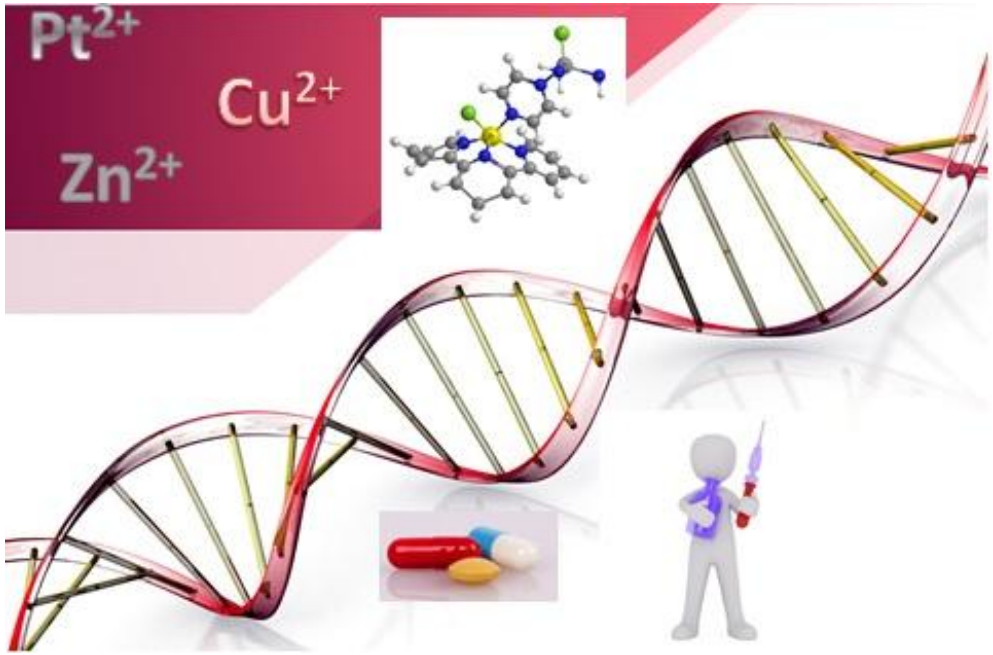
DRŽAVNI UNIVERZITET U NOVOM PAZARU

Novel perspective of anticancer metal-based drugs: Characteristics of heterometallic complexes and their potential applications



Abstract: Platinum-based drugs are widely use in medical treatments, but their effectiveness is limited by toxicity. The mechanism of actions is well known, while side effects could be explained by interactions of platinum (soft acid) with biomolecules, which contain sulfur as donor atom (soft bases), such as thiols and the thioethers. One of the possible ways to overcome these limitations could be designing novel heterometallic complexes with metal centers that have different coordination geometry, kinetics properties, affinity, and reactivity towards biological relevant nucleophiles. According to hard-soft acid base principle, dissimilar reactivity of metal centers will result in different coordination modes of biomolecules and in increment of cytotoxicity.

The novel heterometallic complexes: [{*cis*-PtCl(NH_3)(μ-pyrazine)ZnCl(terpy)}](ClO_4)$_2$ (Pt-L1-Zn), [{*cis*-PtCl(NH_3)(μ-4,4′-bipyridyl)ZnCl(terpy)}](ClO_4)$_2$ (Pt-L2-Zn), [{ZnCl(terpy)(μ-pyrazine)CuCl(terpy)}](ClO_4)$_2$ (Zn-L1-Cu), [{ZnCl(terpy)(μ-4,4′-bipyridyl)CuCl(terpy)}](ClO_4)$_2$ (Zn-L2-Cu) (terpy = 2,2′:6′,2′′-terpyridine, L1 = pyrazine, L2 = 4,4′-bipyridyl) were synthesized and characterized. The investigation of the interactions between complexes and biomolecules under physiological conditions has pointed out that heterometallic complexes with two different metal centers have great influence on the order of the reactivity and different coordination modes of biomolecules. The investigation of cytotoxic activity has shown that all complexes significantly reduced cell viability on human colorectal cancer cell line (HCT-116) and human breast cancer cell line (MDA-MB-231) lines and exerted significant cytotoxic effects, with better effect on HCT-116 cells than cisplatin, especially after 72 h.

Keywords: zinc(II); platinum(II); copper(II); heterometalic complexes;

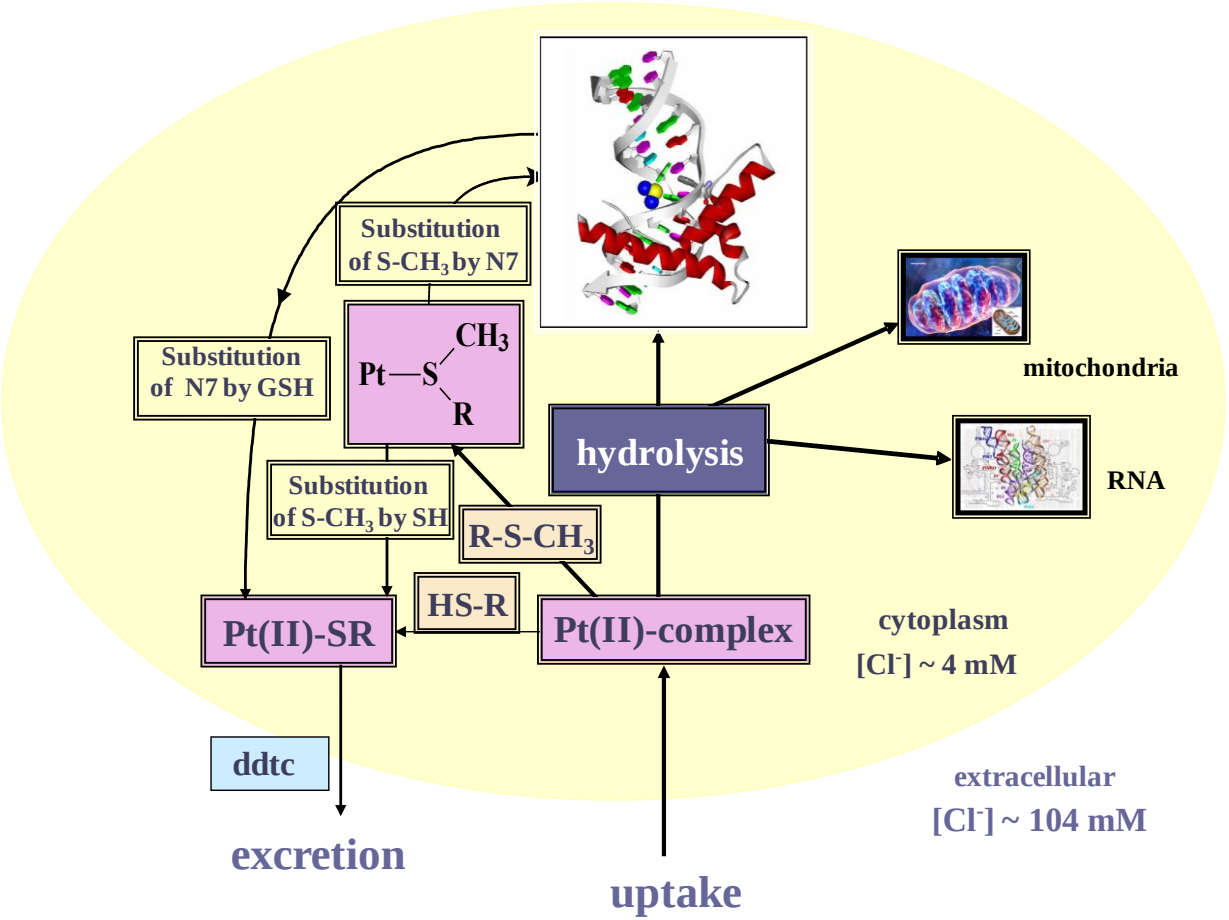
Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, with lung cancer on the first place.

One of eternal goal of medicinal chemistry is to find more effective ways to treat cancer and extend human beings' life as long as possible.

Discovery of cisplatin was revolutionary in treatment of cancer, but application of cisplatin and other platinum-based drugs is limited due to negative side effects.

Intracell processes during application of platinum-based antitumor agents



The possible ways to overcome limitations of platinum-based drugs could be the design of heterometallic complexes.

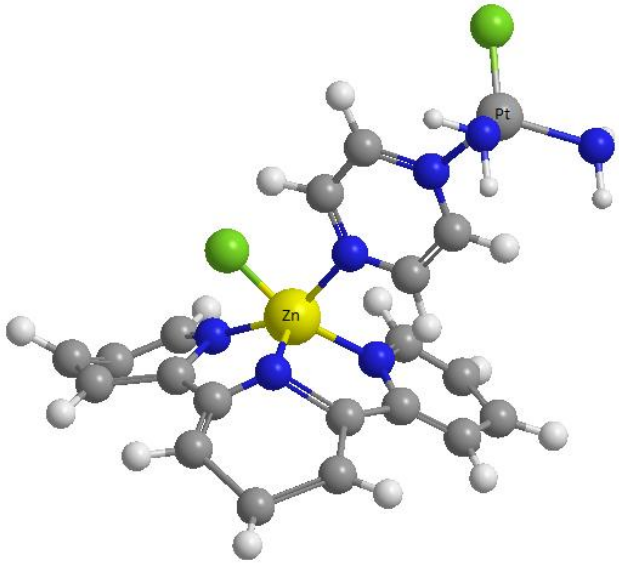
Two different metal centres, differing in Lewis acidity according to HSAB principle, geometry and kinetic characteristics, connected with π-acceptor bridging ligands, could give promising antitumor activity.

HSAB principle could predict bioinorganic reaction mechanism.

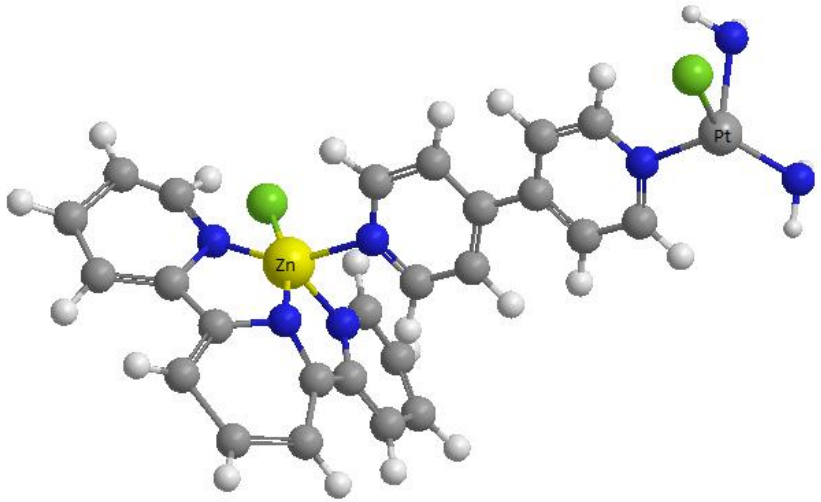
Selected hard and soft metal centers (Lewis acids) and ligands (Lewis bases) and those that exhibit intermediate behavior

Hard (acids)	Intermediate (acids)	Soft (acids)
Li^+, Na^+, K^+, Rb^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Sn^{2+}, Mn^{2+}, Al^{3+}, Ga^{3+}, In^{3+}, Sc^{3+}, Cr^{3+}, Fe^{3+}, Co^{3+}, Y^{3+}, Th^{4+}, Pu^{4+}, Ti^{4+}, Zr^{4+}, $[VO]^{2+}$, $[VO_2]^+$	Pb^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Os^{2+}, Ru^{3+}, Rh^{3+}, Ir^{2+}	Zero oxidation state metal centers, Tl^+, Cu^+, Ag^+, Au^+, $[Hg_2]^{2+}$, Hg^{2+}, Cd^{2+}, Pd^{2+}, Pt^{2+}, Ru^{2+} Tl^{3+}
Hard (bases)	**Intermediate (bases)**	**Soft (bases)**
F^-, Cl^-, H_2O, ROH, R_2O, $[OH]^-$, $[RO]^-$, $[RCO_2]^-$, $[CO_3]^{2-}$, $[NO_3]^-$, $[PO_4]^{3-}$, $[SO_4]^{2-}$, $[ClO_4]^-$, $[ox]^{2-}$, NH_3, RNH_2	Br^-, $[N_3]^-$, py, $[SCN]^-$ (N-bound), $ArNH_2$, $[NO_2]^-$, $[SO_3]^{2-}$	I^-, H^-, R^-, $[CN]^-$ (C-bound), CO (C-bound), RNC, RSH, R_2S, $[RS]^-$, $[SCN]^-$ (S-bound), R_3P, R_3As, R_3Sb, alkenes, arene

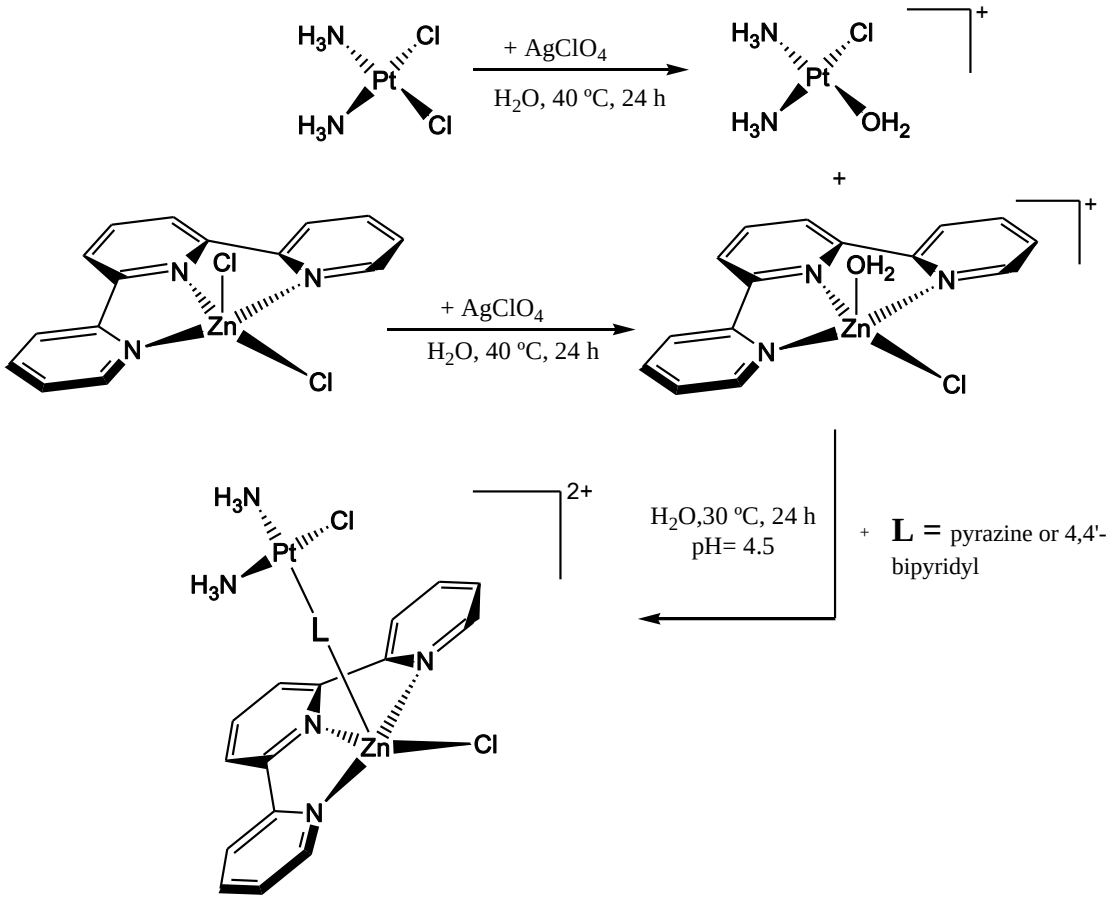
Results and discussion



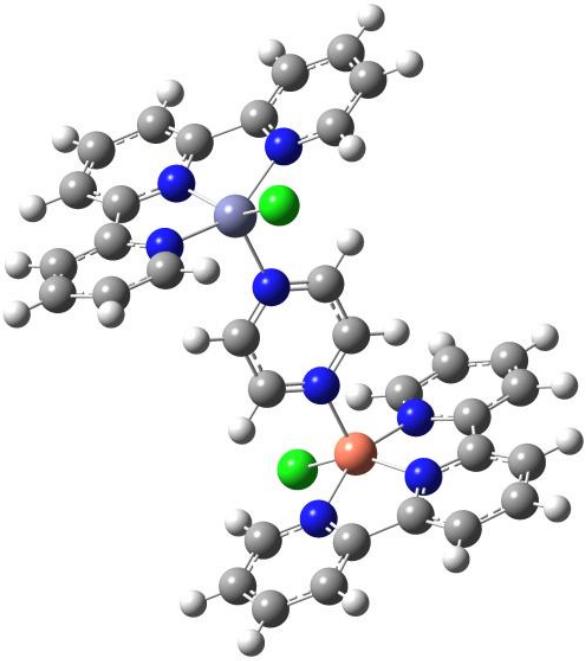
[{*cis*-PtCl(NH_3)(μ-pyrazine)ZnCl(terpy)}](ClO_4)$_2$
(Pt-L1-Zn)



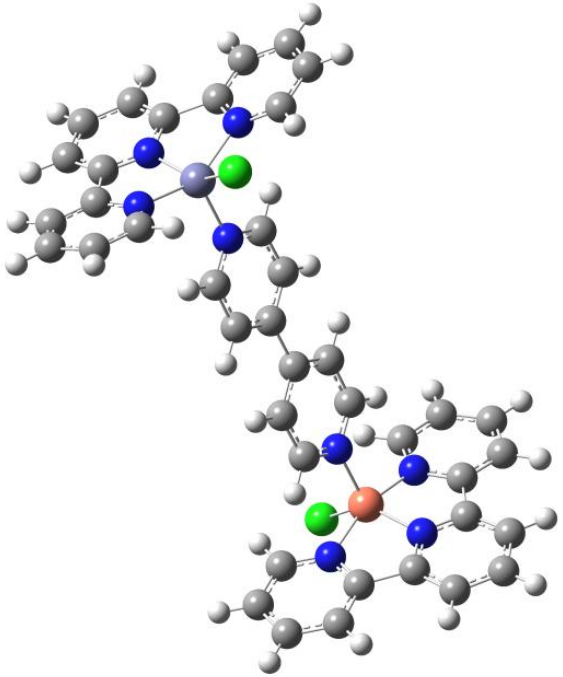
[{*cis*-PtCl(NH_3)(μ-4,4'-bipyridyl)ZnCl(terpy)}](ClO_4)$_2$
(Pt-L2-Zn)



Synthesis of Pt-L-Zn complexes

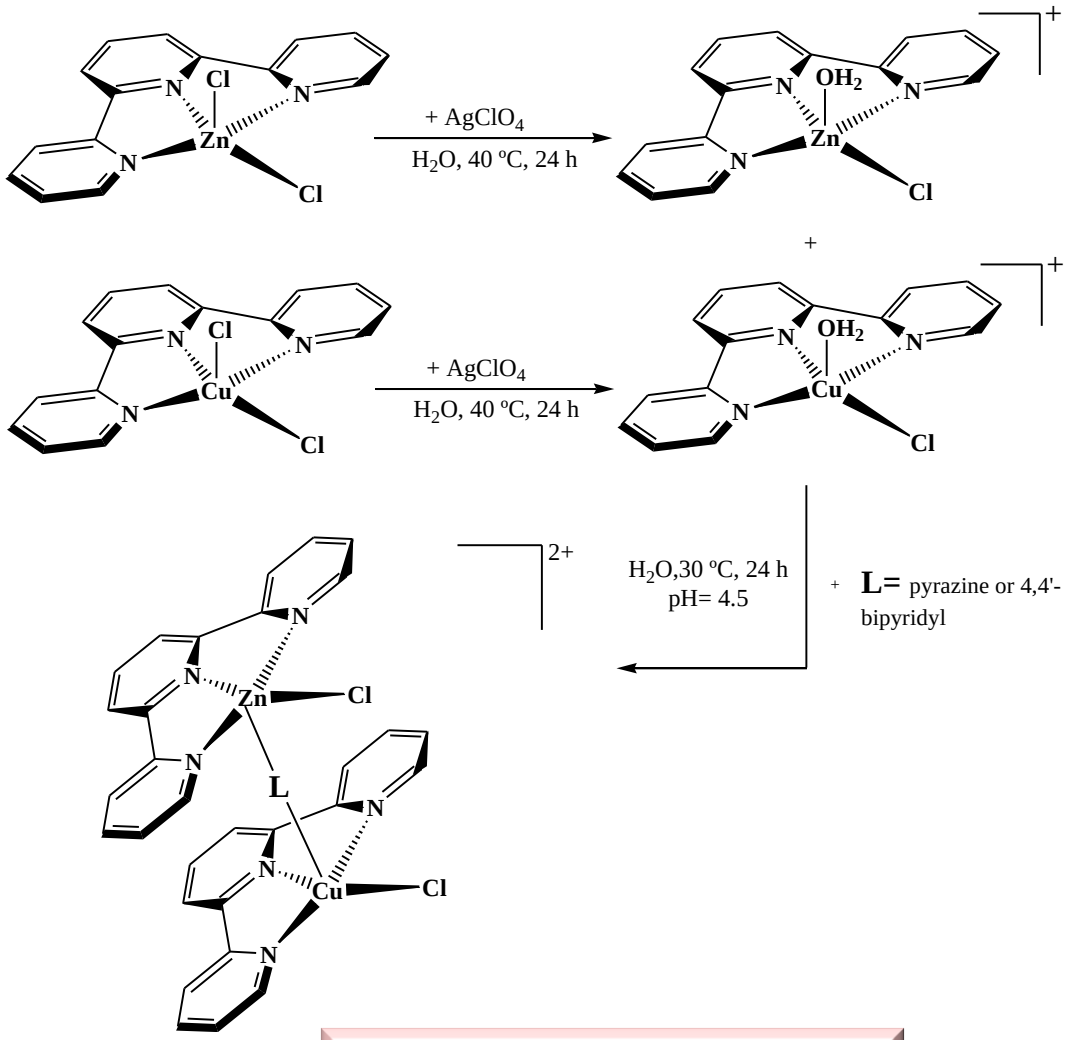


[{ZnCl(terpy)(μ-pyrazine)CuCl(terpy)}]$(ClO_4)_2$
(Zn-L1-Cu)



[{ZnCl(terpy)(μ-4,4′-bipyridyl)CuCl(terpy)}]$(ClO_4)_2$
(Zn-L2-Cu)

terpy = 2,2′:6′,2″-terpyridine, L1 = pyrazine, L2 = 4,4′-bipyridyl



Synthesis of Zn-L-Cu complexes

Summary of p*K*a values for the deprotonation steps of the investigated diaqua complexes

Complex	pK_{a1}	pK_{a2}
Pt-L1-Zn	3.47 ± 0.03	5.19 ± 0.02
Pt-L2-Zn	3.99 ± 0.06	6.97 ± 0.01

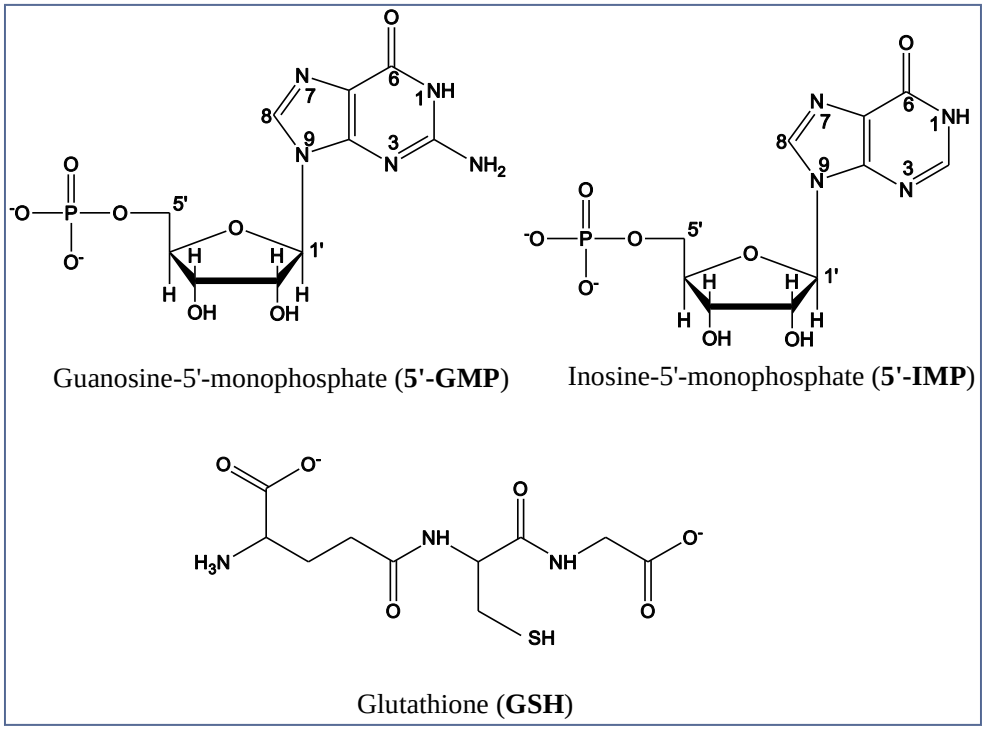
Complex	pK_{a1}	pK_{a2}
Zn-L1-Cu	3.85 ± 0.03	5.99 ± 0.04
Zn-L2-Cu	3.96 ± 0.01	7.03 ± 0.01

Complexes are expected to be stable especially under physiological conditions (approximately pH 7.4), although p*K*a$_2$ of the complexes with 4,4′-bipy bridging ligand are very close to physiological conditions and remain intact (for the comparison pK_a values of cisplatin are 6.85 and 7.87).

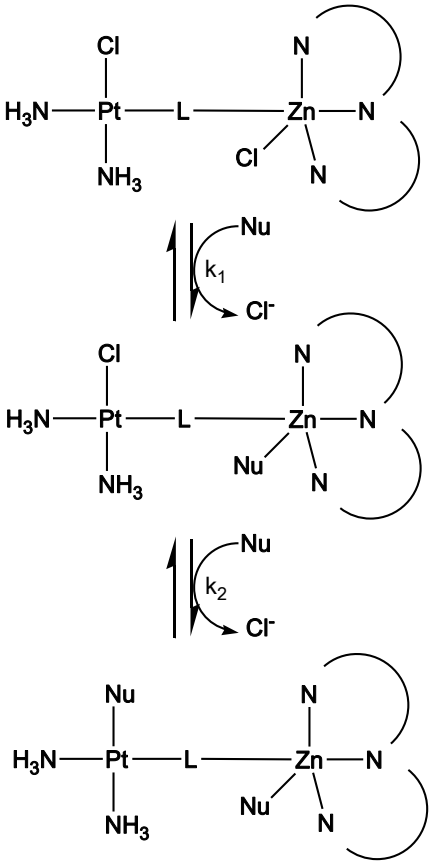
Bioinorganic reactions

- **Under the classification of bioinorganic reactions we consider the interactions of metal ions with biomolecules under physiological conditions.**

- **Ligand affinity and possible coordination geometries of the metal center are important bioinorganic principles. Metal-ligand bonds are closely related to the HSAB nature of metals and their preferred ligands.**

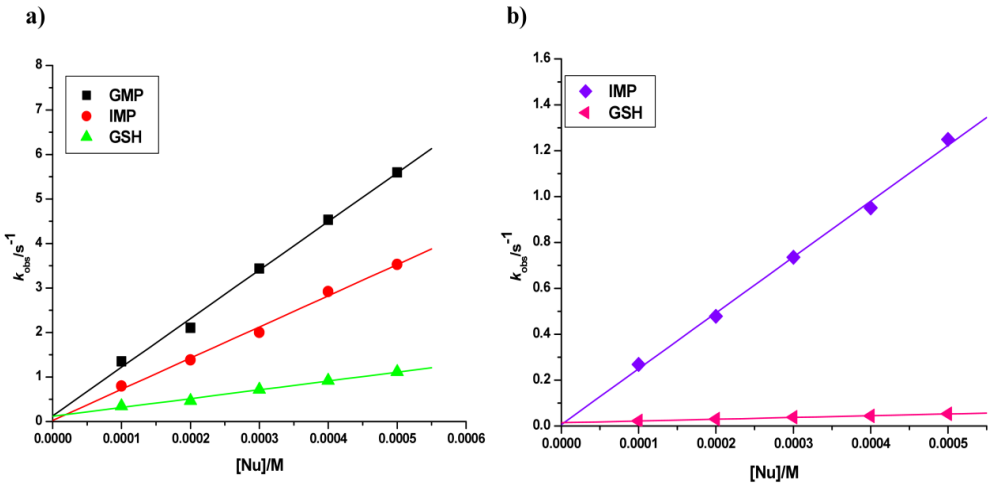


Structures of the investigated biomolecules



Nu = 5'-GMP, 5'-IMP, GSH
L = pyrazine, 4, 4'-bipyridyl

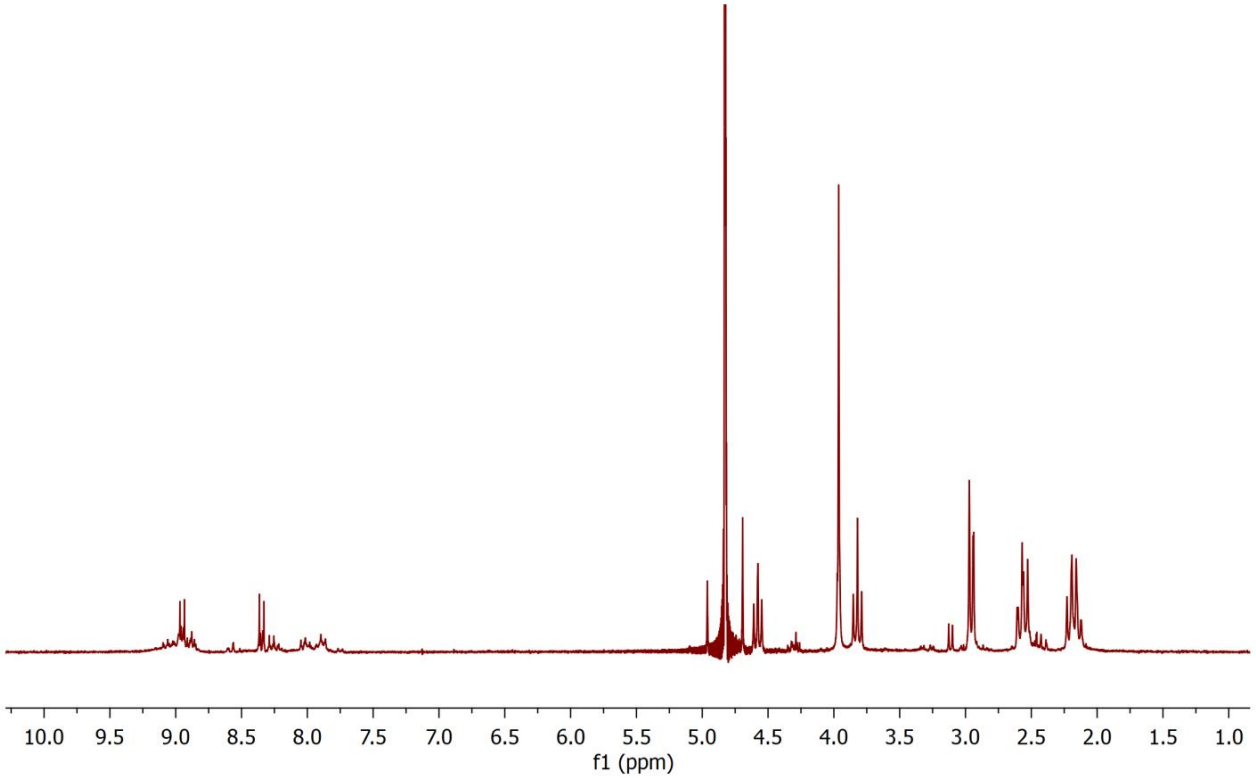
Proposed pathways for the reaction of the heteromerallic Pt-L-Zn complexes with biologically relevant nucleophiles



***Pseudo*-first-order rate constants plotted as a function of nucleophile concentration for the first (a) and second (b) substitution reactions of Pt-L1-Zn complex with 5'-GMP, 5'-IMP and GSH mixing at pH 7.4 (0.010 mol L^{-1} Tris-HCl buffer) in addition of 0.005 mol L^{-1} NaCl at 25 °C**

The order of reactivity of the investigated biomolecules for the first reaction is 5'-GMP > 5'-IMP > GSH, while for the second is 5'-IMP > GSH.

Different coordination modes of biomolecules



^{1}H NMR spectrum of the reaction between Pt-L2-Zn complex with GSH in molar ratio 1:2 in D_2O

Zn-L1-Cu and Zn-L2-Cu complexes

The order of reactivity for Zn-L1-Cu complex is GSH > 5′-IMP > 5′-GMP, while 5′-GMP > GSH > 5′-IMP for Zn-L2-Cu.

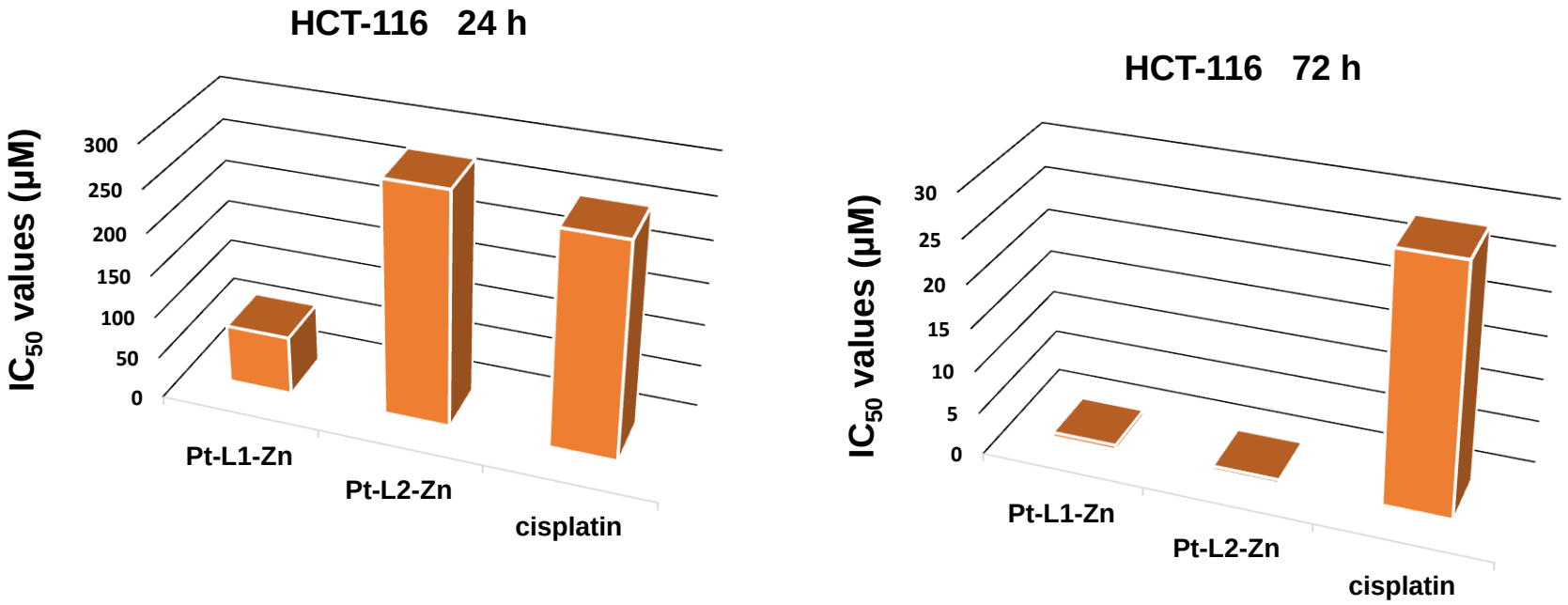
The obtained results indicated that the type of bridging ligand is very important, as well as the presence of inert ligand.

The coordination of both metal centres is square-pyramidal which enables the coordination to different donor atoms such as N7 or phosphate residue from 5′-GMP and 5′-IMP, and *O*-carboxylate from GSH.

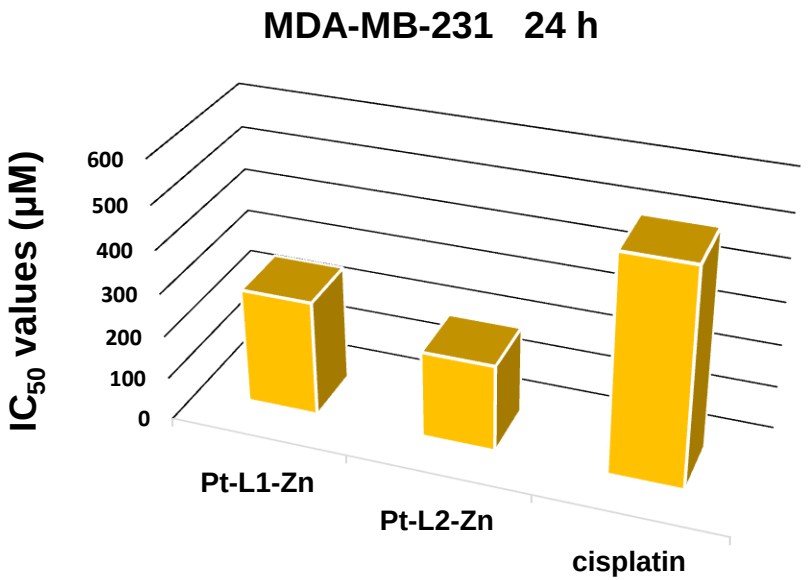
Zinc(II) and cooper(II) ions as borderline hardness Lewis acid display high affinity for nitrogen and oxygen donor atoms when coordination number is 5.

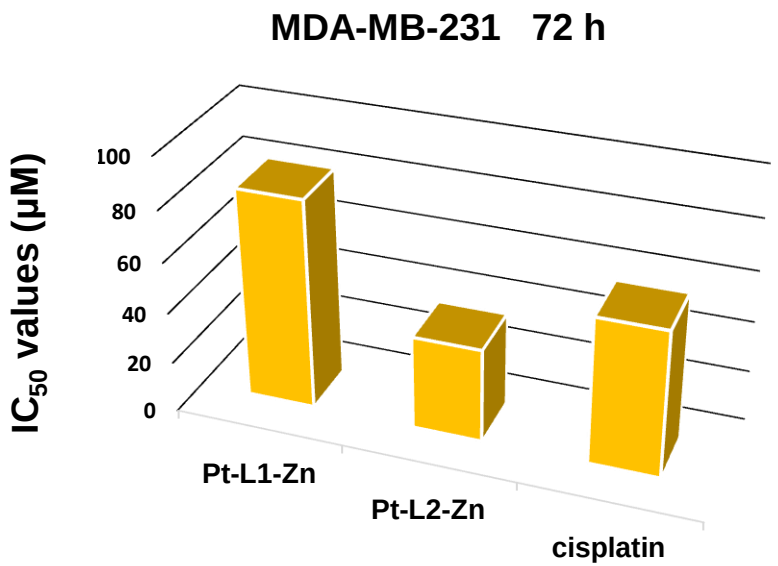
Potential applications

Cytotoxic activity of Pt-L-Zn complexes



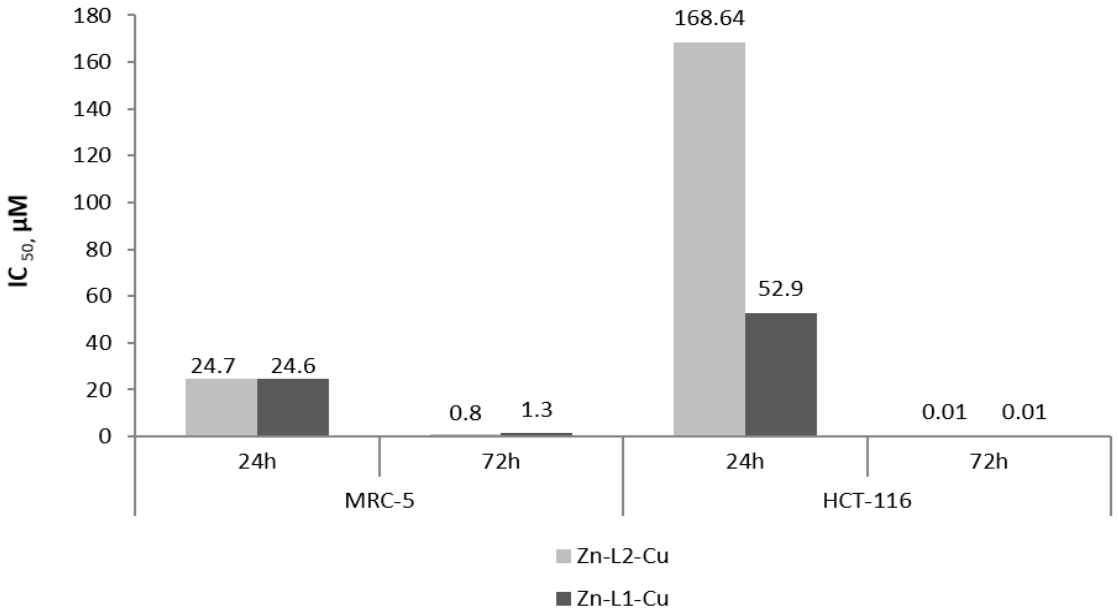
Cytotoxic effects - IC_{50} values (μM) of Pt-L1-Zn and Pt-L2-Zn complexes on HCT-116





Cytotoxic effects - IC_{50} values (µM) of Pt-L1-Zn and Pt-L2-Zn complexes on MDA-MB-231

Cytotoxic activity of Zn(II)-L-Cu(II) complexes



The cytotoxic effects (IC_{50} values) of Zn-L1-Cu and Zn-L2-Cu complexes after 24 h and 72 h exposure

Antimicrobial activity of Zn-L-Cu complexes

Bacterial species	MIC[a]			Fungal species	MIC		
	Zn-L1-Cu	Zn-L2-Cu	Antibiotic[b]		Zn-L1-Cu	Zn-L2-Cu	Antimycotic[c]
Enterococcus faecalis	0.25	0.125	<0.3125	*Trichoderma longibrachiatum*	0.5	0.5	>40
Bacillus subtilis	0.25	0.25	2.5	*Trichoderma harzianum*	0.5	0.25	>40
Bacillus cereus	0.125	0.25	2.5	*Penicillium canescens*	0.5	0.25	20
Pseudomonas aeruginosa	0.0625	0.125	5	*Penicillium cyclopium*	0.5	0.25	2.5
Salmonella enteritidis	0.125	0.0625	<0.3125	*Doratomyces stemonitis*	0.25	0.25	40
Salmonella typhimurium	0.0625	0.125	2.5	*Alternaria alternata*	0.25	0.25	5
Staphylococcus aureus	0.25	0.5	2.5	*Fusarium oxysporum*	1	0.5	10
Staphylococcus epidermidis	0.5	0.5	<0.3125	*Aspergillus brasiliensis*	0.25	0.25	40
Klebsiella pneumoniae	0.0078	0.0078	2.5	**Yeast**			
Escherichia coli	0.25	0.0625	0.625	*Candida albicans*	0.5	0.5	1.25

[a] MIC for compounds as mM, MIC for antibiotic/antimycotic μg/mL; [b]Tetracyclin; [c] Ketoconazole/Nystatin

Conclusions

The heterometallic complexes with two different metal centres, which are different in Lewis acidity, geometry, have great influence on the order of the reactivity and different coordination modes of biomolecules.

The obtained results indicated that the type of bridging ligand is very important, as well as the presence of inert ligand.

Long distance between the different metal centres led to less reactivity of both centres because of reduced electronic communication between them and an increase of electron density on the metal centres.

These complexes were more active on HCT-116 cells, and the reason for better cytotoxicity of Pt-L1-Zn and Pt-L2-Zn complexes against HCT-116 cells after 72 h and Pt-L2-Zn complex against MDA-MB-231 after 72 h than cisplatin, could be correlated with geometrical structures, types of the metal centres, and the nature of bridging ligand.

Zn-L1-Cu and Zn-L2-Cu complexes were active against *Gram negative* bacterial strains, the most sensitive bacteria against both tested complexes were *K. pneumoniae.*

Both Zn-L1-Cu and Zn-L2-Cu complexes induced strong prooxidative response in tested cell lines, which consequently led to strong cytotoxicity and high selectivity.

Overall, we may conclude that heterometallic complexes containing metals centres with different Lewis acidity, geometry, and kinetic characteristics, connected with π-acceptor bridging ligands, could give promising antitumor activity.

Acknowledgments

MINISTRY OF EDUCATION,
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