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Interactions of zinc(II) complexes with N-donor ligands with 5'-GMP and their cytotoxic activity

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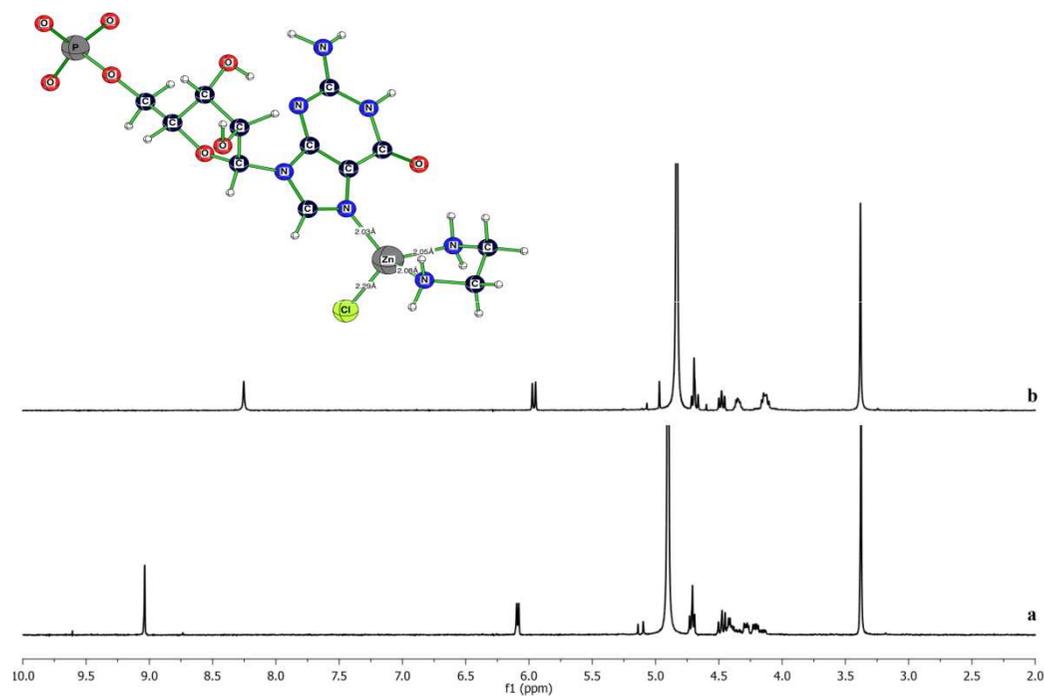
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Interactions of zinc(II) complexes with 5'-GMP and their cytotoxic activity



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Abstract: Design of novel non-platinum DNA and protein targeting metal-based anticancer agents with potential *in vitro* toxicity has gained importance in recent years (Bertini, I. *et al.* Biological Inorganic Chemistry. Structure and Reactivity. *University Science Books. Sausalito, CA. 2007*). The non-platinum antitumor complexes could be alternatives to platinum-based drugs due to their better characteristics and less negative side effects. (Pessoa, J.C., *et al.* *J. Inorg. Biochem.* **2011**, 105, 637-644).

The mechanism of substitution from tetrahedral $[\text{ZnCl}_2(\text{en})]$ and square-pyramidal $[\text{ZnCl}_2(\text{terpy})]$ complexes (where en = 1,2-diaminoethane or ethylenediamine; terpy= 2,2':6',2''-terpyridine) by guanosine-5'-monophosphate (5'-GMP) has been investigated by ^1H NMR spectroscopy. Information about the structures of the final products in solution were obtained from the DFT calculations (B3LYP/6-31G(d)) and experimental ^1H NMR data acquired during the course of the reaction. The cytotoxic activity of zinc(II) complexes was tested on human breast cancer cell line MDA-MB-231, human colon cancer cell line HCT-116 and normal human lung fibroblast cell line MRC-5. Both complexes reduced cell viabilities, while $[\text{ZnCl}_2(\text{terpy})]$ complex was significantly cytotoxic on MDA-MB-231 after 72 h, and HCT-116 after 24 h without dose dependence. The differences in reactivity toward 5'-GMP and cytotoxic activity of Zn(II) complexes may be attributed to the very stable square-pyramidal geometry of $[\text{ZnCl}_2(\text{terpy})]$ complex in solution, while weak ligand effect of the en compared to the terpy affected slow interaction of tetrahedral $[\text{ZnCl}_2(\text{en})]$ complex with the target bio-molecule (Soldatović, E., *et al.* *J. Coord. Chem.* **2019**, 72(4), 690-706).

Keywords: Zinc(II) complexes; guanosine-5'-monophosphate; ^1H NMR; DFT calculations; structure – reactivity correlation; anticancer cytotoxic activity



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Introduction

- ❖ The non-platinum antitumor complexes could be alternatives to platinum-based drugs due to their better characteristics and less negative side effects.
- ❖ Some transition metal ions are essential cellular components involved in several biochemical processes. They act mainly as Lewis acids, having unique characteristics such as redox activity, variable coordination modes, kinetics properties and reactivity towards biological relevant nucleophiles. Due to their characteristics and roles in physiological processes, the compounds of essential transition metals could be more effective as drugs in treatment of cancers.
- ❖ Zinc(II) has a specific role in bioinorganic processes. Zinc(II) complexes have also shown potential utilization as radioprotective agents, antibacterial or antimicrobial agents, antidiabetic insulin-mimetic and tumor photosensitizers.
- ❖ Knowledge of the mechanism of interactions between zinc(II) complexes and bio-molecules or other relevant ligands is essential for understanding the cellular biology of delivery of complexes to DNA and proteins and gives valuable information for the synthesis of new drug

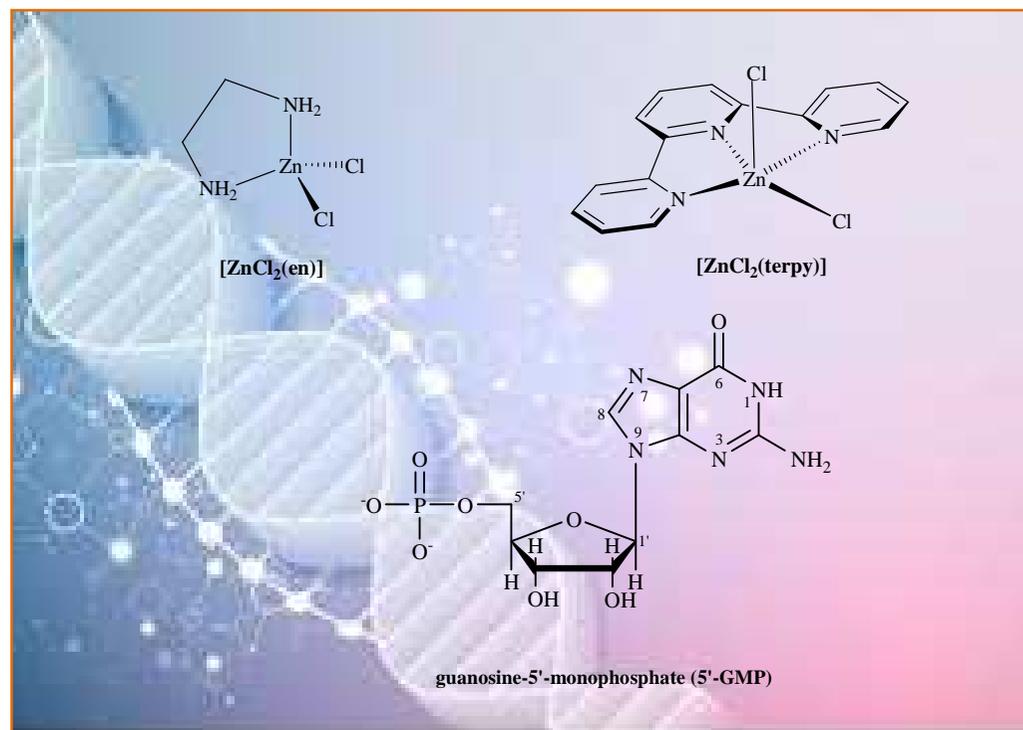


Results and discussion

✓ An attempt has been made to understand the mechanism of substitution between DNA constituent 5'-GMP and the tetrahedral $[\text{ZnCl}_2(\text{en})]$ and square-pyramidal $[\text{ZnCl}_2(\text{terpy})]$ complexes.

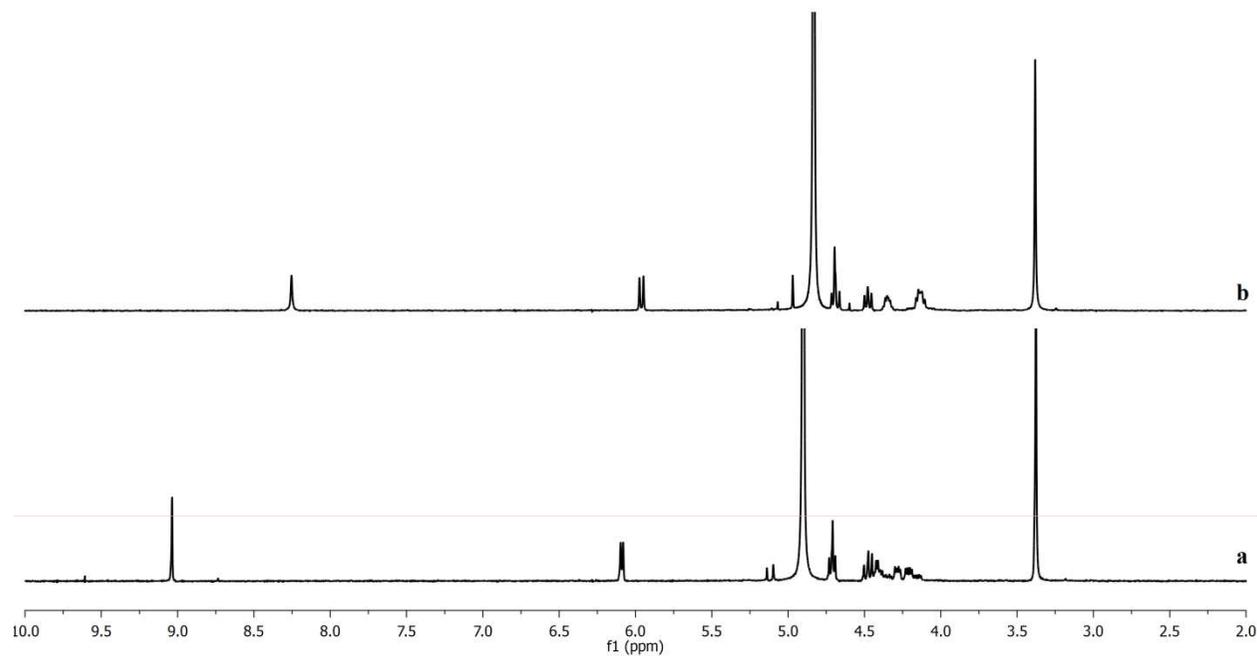
✓ DFT calculations (B3LYP(CPCM)/-6-311+G**) have been used in combination with NMR spectroscopic data to solve the structures of formed complexes.

✓ Another aim of this study was also to evaluate the cytotoxic effect of Zn(II) complexes on human breast cancer cell line (MDA-MB-231), human colon cancer cell line (HCT-116) and normal human lung fibroblast cell line (MRC-5).



Structures of the investigated complexes and nucleophiles





*NMR spectra of the reaction between $[ZnCl_2(en)]$ and 5'-GMP at 295 K, pH 4.5 in D_2O :
a) spectrum at initial time; b) spectrum obtained after 48 h.*



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Experimental $^1\text{H-NMR}$ shifts (δ ppm) relative to TSP in D_2O and calculated (B3LYP(CPCM)/-6-311+G**) shifts with selected bond distances [\AA] of the calculated (B3LYP/6-31G*) structural data.

| Compound | $[\text{ZnCl}(\text{2,2':6',2''-terpyridina})(\text{N7-GMP})]$ | | | | | $[\text{ZnCl}(\text{en})(\text{N7-GMP})]$ | | | $[\text{ZnCl}_2(\text{en})(\text{N7-GMP})]$ | | | |
|--------------|--|----------|-----------|---------|----------|---|--------------------------|----------|---|--------------------------|----------|-----------|
| | H(6,6'') | H(5,5'') | H(4,4'') | H(3',5) | H(8)-GMP | H(1')-GMP | $\text{NH}_2(\text{en})$ | H(8)-GMP | H(1')-GMP | $\text{NH}_2(\text{en})$ | H(8)-GMP | H(1')-GMP |
| Experimental | 8.95 | 7.71 | 8.49-8.42 | 8.70 | 4.85 | | 4.97 | 8.25 | 5.90 | 4.97 | 8.25 | 5.90 |
| Calculated | 8.93 | 7.11 | 8.18 8.02 | 8.22 | 4.85 | | 4.45 | 7.64 | 5.52 | 3.72 | 6.27 | 3.36 |

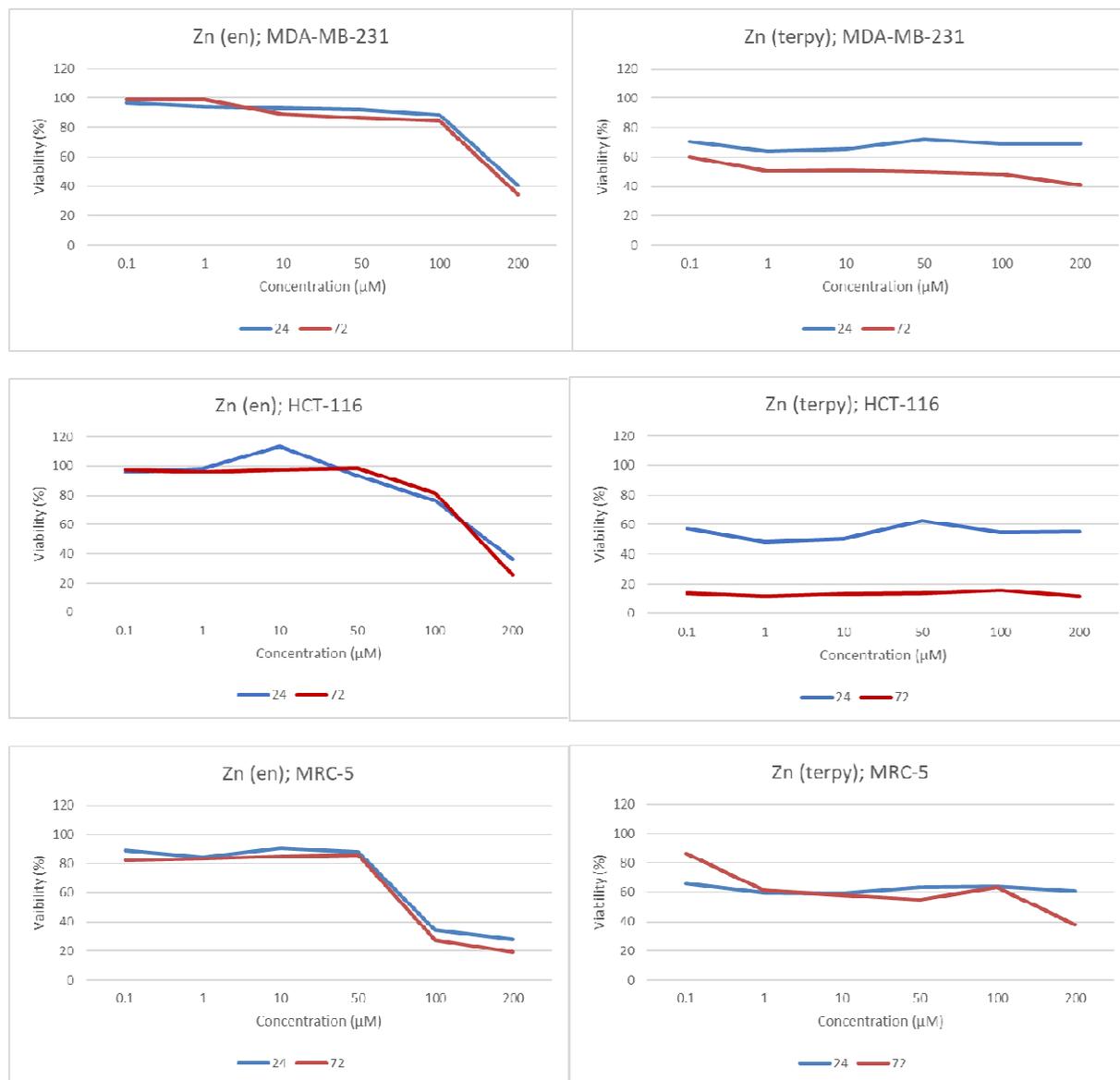
| Bond distances [\AA] | | | |
|---------------------------------|------------------|------------|------------|
| $d(\text{Zn-N})$ | 2.18, 2.11, 2.24 | 2.05, 2.08 | 2.11, 2.13 |
| $d(\text{Zn-Cl})$ | 2.32 | 2.29 | 2.72 |
| $d(\text{Zn-N7-GMP})$ | 2.06 | 2.03 | 2.08 |



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The effect of [ZnCl₂(en)] (left) and [ZnCl₂(terpy)] (right) complexes on MDA-MB-23, HCT-116 and MRC-5 cells viability after 24 and 72 h of exposure. All values are mean, n=6; percentages of viable cells.



Coefficient of correlation (R) between concentrations of zinc(II) complexes and cytotoxic effect on MDA-MB-23, HCT-1161 and MRC-5 cell lines after 24 and 72 hours incubation. Results are calculated upon percentages of viable cells.

| complex | Coefficient of correlation (R) | | | | | |
|-----------|--------------------------------|----------|----------|----------|---------|---------|
| | MDA-MB-231 | | HCT-116 | | MRC-5 | |
| | 24 h | 72 h | 24 h | 72 h | 24 h | 72 h |
| Zn(en) | -0.920** | -0.946** | -0.956** | -0.941** | -0.907* | -0.907* |
| Zn(terpy) | 0.301 | -0.835* | 0.199 | -0.08 | -0.075 | -0.728 |

Cytotoxic effects - IC₅₀ values (μM) of zinc(II) complexes on HCT-116, MDA-MB-231 and MRC-5 cell lines after 24 and 72 h exposure. Results are calculated upon percentages of viable cells.

| complex | IC ₅₀ | | | | | |
|-----------|------------------|-------|---------|-------|-------|------|
| | MDA-MB-231 | | HCT-116 | | MRC-5 | |
| | 24 h | 72 h | 24 h | 72 h | 24 h | 72 h |
| Zn(en) | 196.6 | 154.5 | 160.2 | 149.7 | 72.1 | 87.7 |
| Zn(terpy) | x | 23.0 | 10 | x | x | 94.0 |

x – undefined



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Conclusions

- *The results have shown that $[\text{ZnCl}_2(\text{terpy})]$ react very fast in comparison with $[\text{ZnCl}_2(\text{en})]$. The substitution reaction between $[\text{ZnCl}_2(\text{en})]$ and 5'-GMP reached completion after 48 hours.*
- *Different rates of substitution from the Zn(II) complexes by 5'-GMP could be explained by different geometrical structures of these complexes in solution and the presence of pre-equilibrium between tetrahedral and square-pyramidal structure of $[\text{ZnCl}_2(\text{en})]$ complex in solution. Also the type of chelate ligand such as terpy enable electronic communication between three pyridine rings causes a decrease in electronic density on the zinc centre due additional formation of π -back bond and makes it more electrophilic and more reactive.*
- *The final products of the reactions have been fully optimized by DFT method (B3LYP(CPCM)/-6-31G*). Results are in good agreement with the experimental NMR data for $[\text{ZnCl}(\text{en})(\text{N7-GMP})]$ and $[\text{ZnCl}(\text{terpy})(\text{N7-GMP})]$ complexes, calculated structural index τ indicated tetrahedral and square-planar structures of final products, respectively. Both complexes reduced MDA-MB-231, HCT-116 and MRC-5 cell viabilities.*
- *Complex $[\text{ZnCl}_2(\text{terpy})]$ is significantly cytotoxic on MDA-MB-231 after 72 h, and HCT-116 after 24 h and have not shown dose dependence. The obtained results indicate that the geometry of zinc(II) complexes and the nature of the chelate ligand play the important role in substitution reactions between Zn(II) complexes and biological relevant nucleophiles, as well as in their anticancer activity. This study could provide very useful information for the future design of potential zinc-based anticancer drugs.*



Acknowledgments

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