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## *In Vitro* DNA Damage Protection Activity of Four Novel Bridged Dinuclear Cis- and Transplatin-L-Zn(terpy) Complexes

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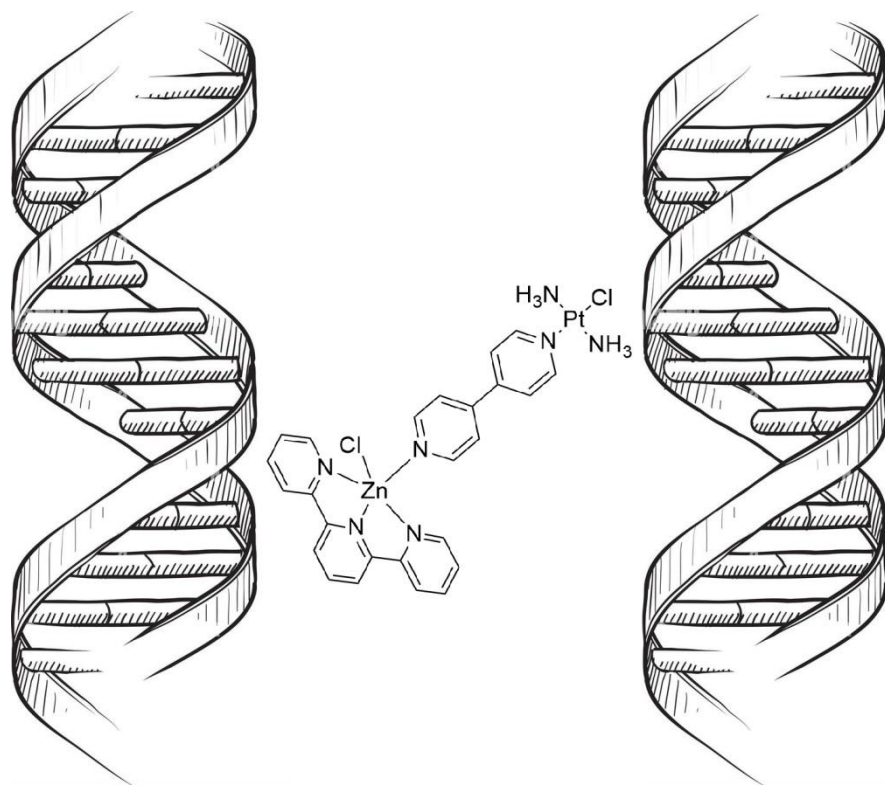
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# ***In Vitro* DNA Damage Protection Activity of Four Novel Bridged Dinuclear Cis- and Transplatin-L-Zn(terpy) Complexes**



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## Abstract

For investigation of *in vitro* DNA damage protection activity four novel dinuclear cis- and transplatin-L-Zn(terpy), where bridging ligand L = pyrazine or 4,4'-bipyridyl, were synthesized. DNA protective effect of the complexes at various concentrations (25, 50, 100, 200, and 400  $\mu\text{g}/\text{mL}$ ) against the hydroxyl and peroxy radicals-induced DNA damage were determined using two different *in vitro* antioxidant assays. Dinuclear complexes exhibited moderate to high DNA-protective effects which depend on the geometry of  $[\text{PtCl}_2(\text{NH}_3)_2]$  complexes as well as the type of the bridging ligand.

**Keywords:** cisplatin; DNA damage; hydroxyl radical; peroxy radical; transplatin; Zn(terpy) complexes



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## Introduction

The physiological interaction between methionine, an essential amino acid in human, and cisplatin and transplatin, platinum-containing antitumor agents, in aqueous solution has been performed recently. The reaction between those two components has been shown to form monofunctional complexes,  $[\text{PtCl}(\text{NH}_3)_2\text{Met}]^+$ . However, distinct features of complexation formation have revealed the cisplatin attack towards methionine, whereas transplatin displays a balance between nitrogen and sulfur-binding (Paciotti et al., 2017). The adducts formed by coordination to DNA could be monofunctional, intra- and interstrand cross-link and protein-DNA adducts. Thus, the DNA adducts formed by *cis*- and *trans*-Pt(II) complexes are quite distinct.

A comparative study of *cis*- and *trans*-platinum(II) dinuclear bridged complexes was performed in order to investigate the influence of the geometry of the Pt(II) complexes, as well as the type of bridging ligand in dinuclear complexes with Zn(terpy) units on DNA protective activity.

Paciotti, R, Corinti D, De Petris A, et al., Cisplatin and transplatin interaction with methionine: bonding motifs assayed by vibrational spectroscopy in the isolated ionic complexes, *Phys. Chem. Chem. Phys.*, 2017, **19**, 26697-26707.



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## Results and discussion

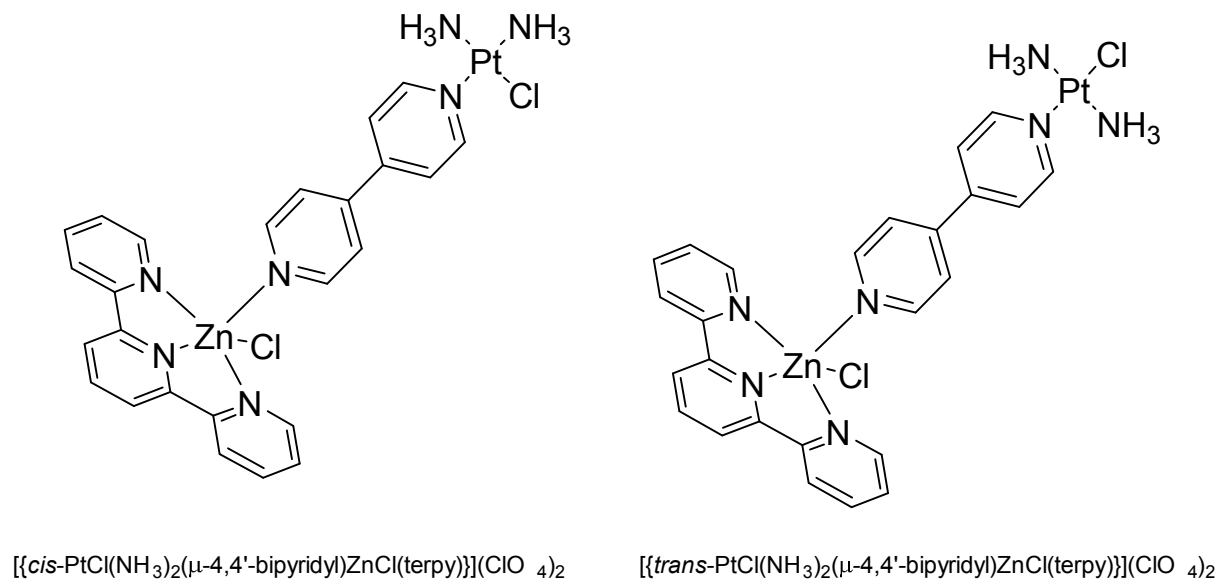
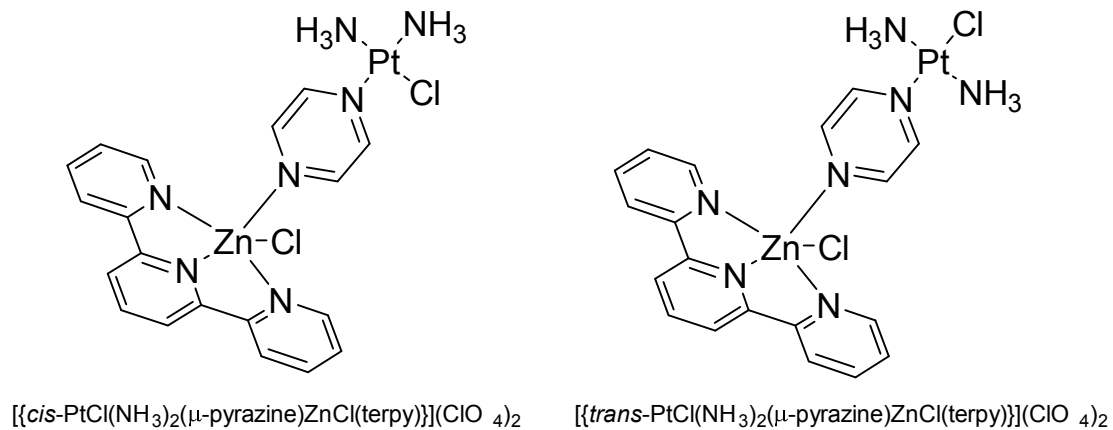
Four novel hetero dinuclear bridged complexes [*cis*- and *trans*-PtCl(NH<sub>3</sub>)<sub>2</sub>(μ-pyrazine)ZnCl(terpy)](ClO<sub>4</sub>)<sub>2</sub> and [*cis*- and *trans*-PtCl(NH<sub>3</sub>)<sub>2</sub>(μ-4,4'-bipyridyl)ZnCl(terpy)](ClO<sub>4</sub>)<sub>2</sub> were synthesized according to a previously published procedure and characterized by elemental analysis, IR and MAS spectroscopy (Soldatović et al., 2020). These heteronuclear complexes differ in geometry of the Pt(II) complex unit and in the type of bridging ligand. The structures of all synthesized complexes are given in Figure 1.

Soldatović, TV, Selimović, E, Milivojević, N, Jovanović, M, Šmit, B., Novel heteronuclear Pt (II)-L-Zn (II) complexes: synthesis, interactions with biomolecules, cytotoxic properties. Two metals give promising antitumor activity? *Appl. Organomet. Chem.*, 2020; **34**: e5864. <https://doi.org/10.1002/aoc.5864>



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**Figure 1.** Four novel dinuclear *cis*- and *trans*platin-L-Zn(terpy), where bridging ligand L = pyrazine or 4,4'-bipyridyl



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The protective activity of four novel heterodinuclear cis- and transplatin-L-Zn(terpy) (where bridging ligand L = pyrazine or 4,4'-bipyridyl) at various concentrations (25, 50, 100, 200, and 400  $\mu\text{g/mL}$ ) against hydroxyl radical-induced DNA damage was assayed *in vitro* using DNA from herring sperm as a model system,  $\text{FeSO}_4$  and  $\text{H}_2\text{O}_2$  for the generation of hydroxyl radicals and quercetin (100  $\mu\text{M}$ ) as reference compound as previously described by Katanić et al. (2019).

The protective effect of four novel heterodinuclear cis- and transplatin-L-Zn(terpy) (where bridging ligand L = pyrazine or 4,4'-bipyridyl) (25, 50, 100, 200, and 400  $\mu\text{g/mL}$ ) against peroxy radical-induced DNA damage was assessed as previously described by Zhang et al. (2017) using (2-methylpropionamidine) dihydrochloride (AAPH) for oxidative damage of DNA.

The DNA bands were visualized using UV transilluminator (Vilber Lourmat, France) at 365 nm, photographed and recorded using ImageJ software (version 1.48 for Windows, Softonic International, Barcelona, Spain). The results are given in Figures 2-5.

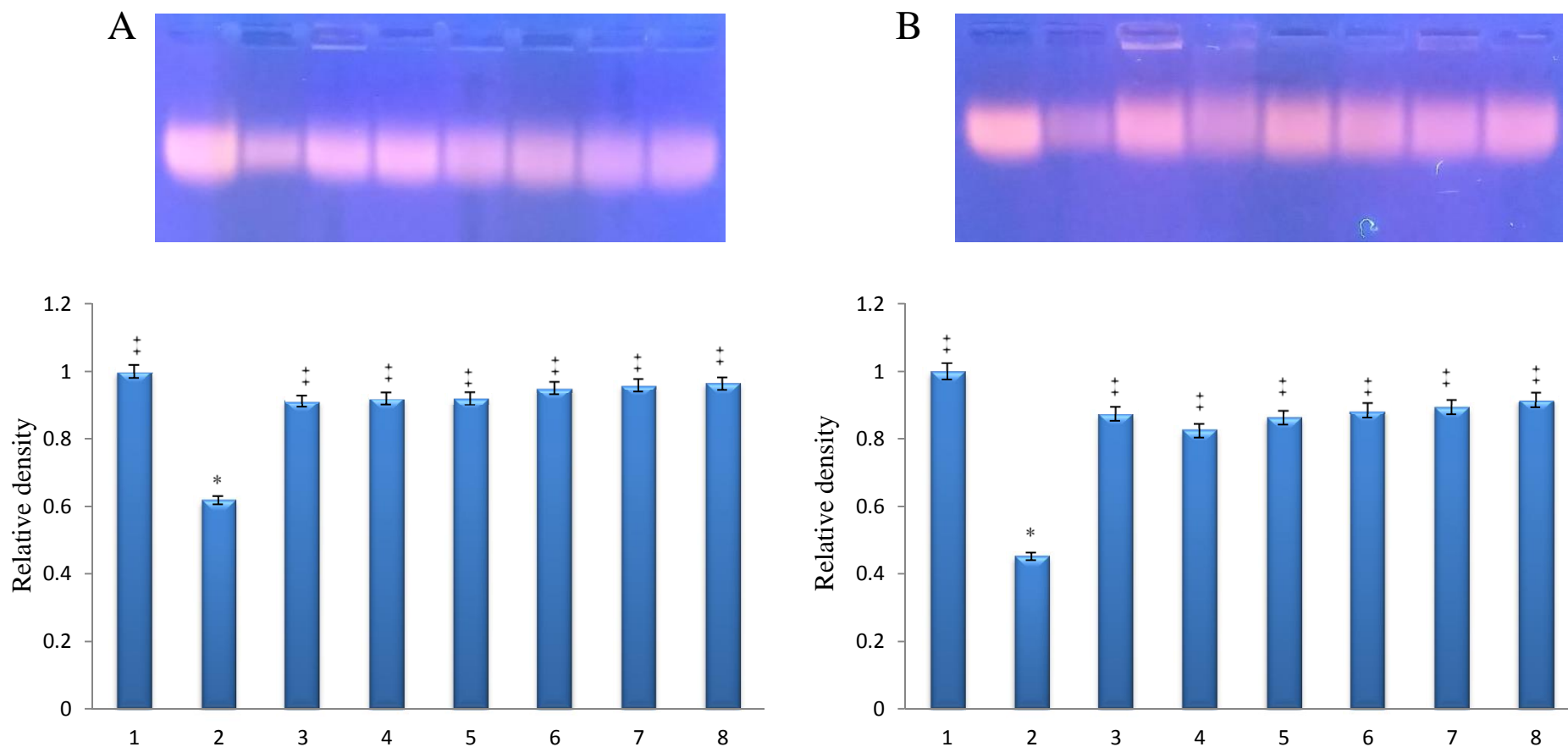
Katanić, J, Yousfi, F, Caruso, MC, Matic, S, Monti, DM, Loukili, EH, Boroja, T, Mihailović, V, Galgano, F, Imbimbo, P, Petruke, G, Bouhrim, M, Bnouham, M, Ramdani, M, Characterization of bioactivity and phytochemical composition with toxicity studies of different *Opuntia dillenii* extracts from Morocco, *Food Biosci.*, 2019, **30**, 100410.

Zhang, LL, Zhang, LF, Xu, JG, Hu, QP, Comparison study on antioxidant, DNA damage protective and antibacterial activities of eugenol and isoeugenol against several foodborne pathogens, *Food Nutr. Res.*, 2017, **61**, 1353356.



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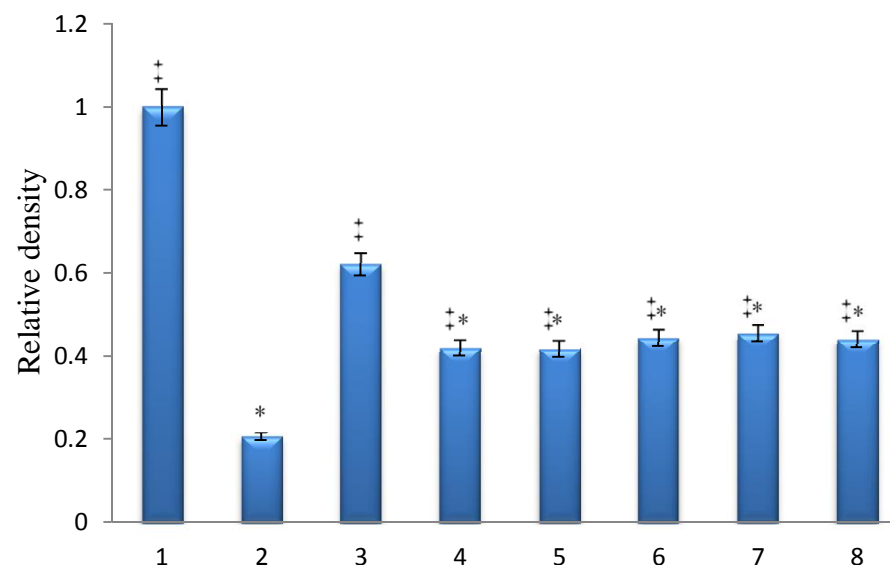
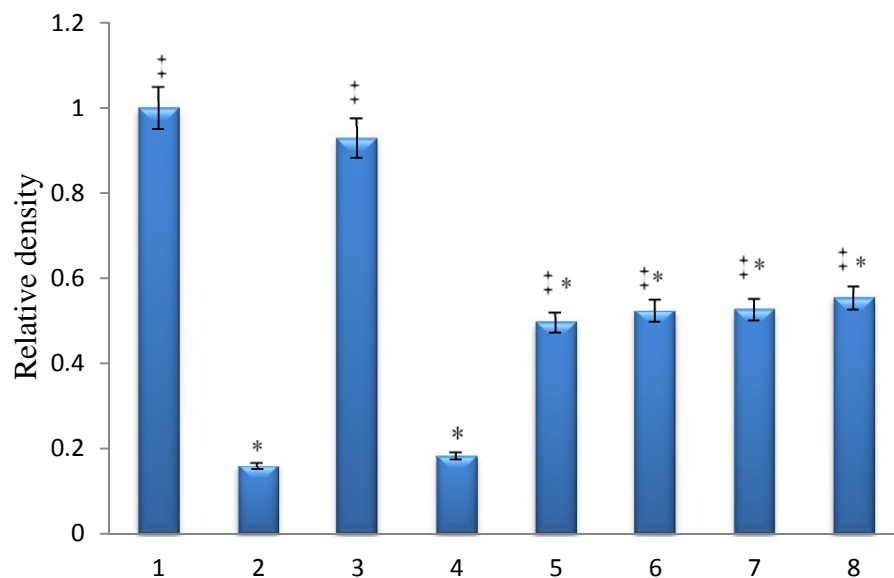
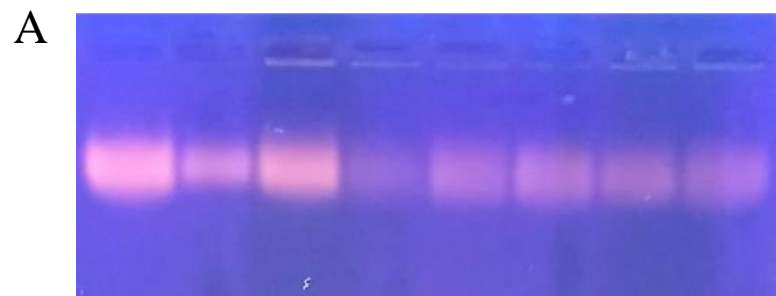
**Figure 2.** Agarose gel electrophoresis of protective effect of  $[\{cis\text{-PtCl}(\text{NH}_3)_2(\mu\text{-pyrazine})\text{ZnCl}(\text{terpy})\}](\text{ClO}_4)_2$  against hydroxyl (A) and peroxy (B) radicals-induced DNA damage. DNA from herring sperm (lane 1, negative control), DNA damage control (lane 2, positive control), quercetin (lane 3, 100  $\mu\text{g}/\text{mL}$ , standard),  $[\{cis\text{-PtCl}(\text{NH}_3)_2(\mu\text{-pyrazine})\text{ZnCl}(\text{terpy})\}](\text{ClO}_4)_2$  at the concentrations of 25, 50, 100, 200, and 400  $\mu\text{g}/\text{mL}$  (lanes 4-8). \* $p < 0.05$  when compared with the negative control group;  $^{\dagger}p < 0.05$  when compared with the positive control group.



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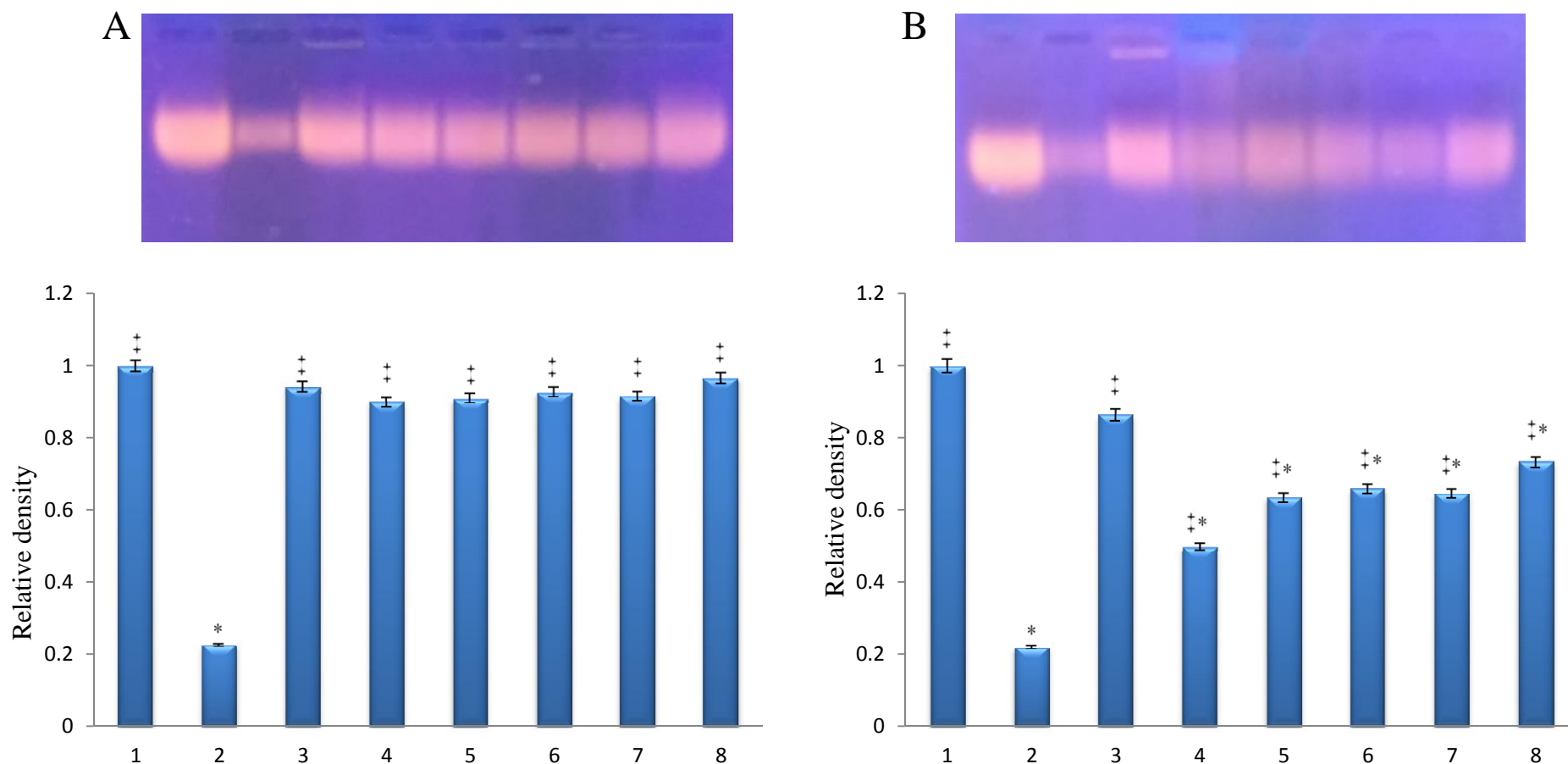


**Figure 3.** Agarose gel electrophoresis of protective effect of  $[[trans-PtCl(NH_3)_2(\mu-4,4'-bipyridyl)ZnCl(terpy)]](ClO_4)_2$  against hydroxyl (A) and peroxy (B) radicals-induced DNA damage. DNA from herring sperm (lane 1, negative control), DNA damage control (lane 2, positive control), quercetin (lane 3, 100  $\mu\text{g}/\text{mL}$ , standard),  $[[trans-PtCl(NH_3)_2(\mu-4,4'-bipyridyl)ZnCl(terpy)]](ClO_4)_2$  at the concentrations of 25, 50, 100, 200, and 400  $\mu\text{g}/\text{mL}$  (lanes 4-8). \* $p < 0.05$  when compared with the negative control group; † $p < 0.05$  when compared with the positive control group.



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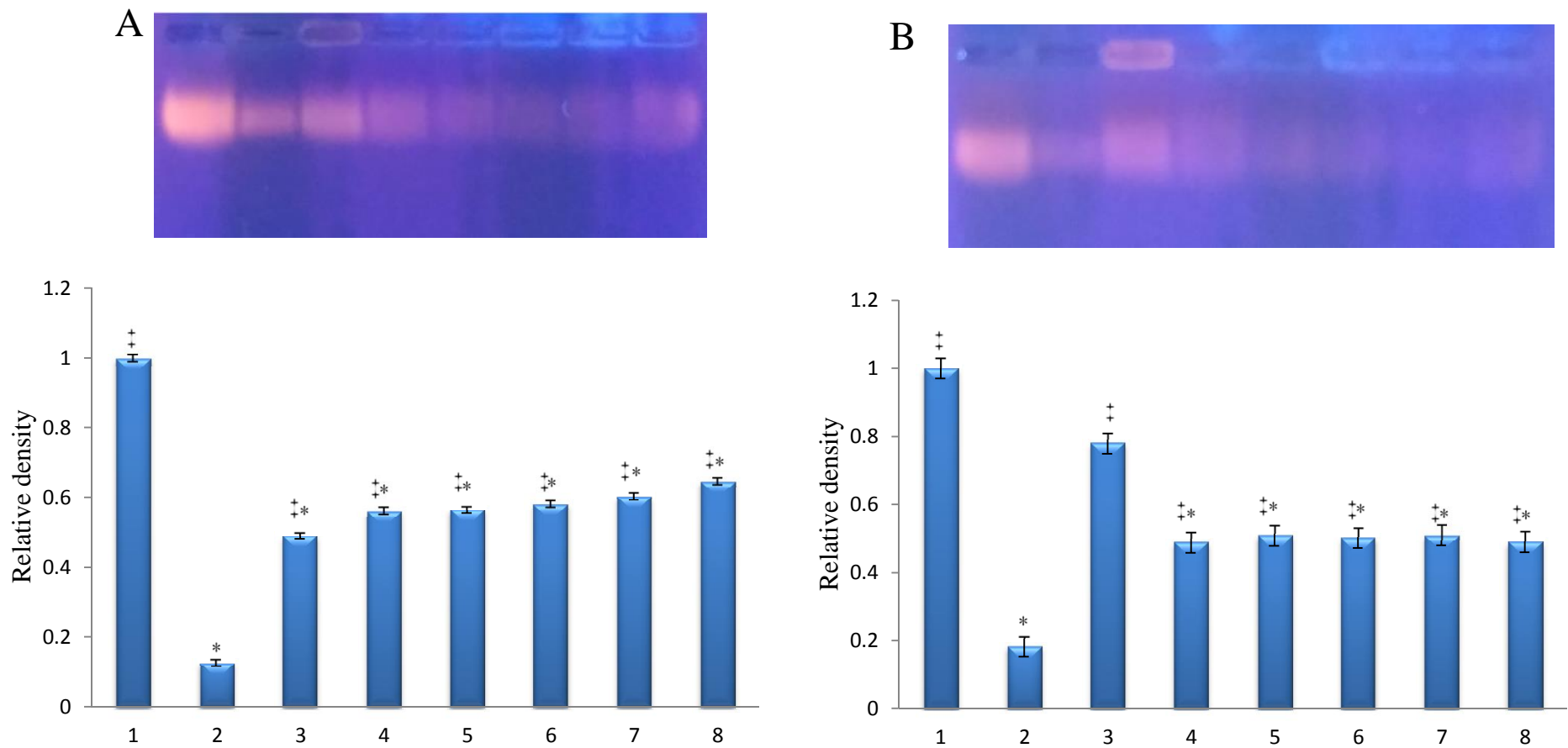


**Figure 4.** Agarose gel electrophoresis of protective effect of  $[[trans\text{-PtCl}(\text{NH}_3)_2(\mu\text{-pyrazine})\text{ZnCl}(\text{terpy})]](\text{ClO}_4)_2$  against hydroxyl (A) and peroxy (B) radicals-induced DNA damage. DNA from herring sperm (lane 1, negative control), DNA damage control (lane 2, positive control), quercetin (lane 3, 100 µg/mL, standard),  $[[trans\text{-PtCl}(\text{NH}_3)_2(\mu\text{-pyrazine})\text{ZnCl}(\text{terpy})]](\text{ClO}_4)_2$  at the concentrations of 25, 50, 100, 200, and 400 µg/mL (lanes 4-8). \* $p < 0.05$  when compared with the negative control group; † $p < 0.05$  when compared with the positive control group.



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**Figure 5.** Agarose gel electrophoresis of protective effect of  $[[cis\text{-PtCl}(\text{NH}_3)_2(\mu\text{-4,4'}\text{-bipyridyl})\text{ZnCl}(\text{terpy})]](\text{ClO}_4)_2$  against hydroxyl (A) and peroxy (B) radicals-induced DNA damage. DNA from herring sperm (lane 1, negative control), DNA damage control (lane 2, positive control), quercetin (lane 3, 100  $\mu\text{g}/\text{mL}$ , standard),  $[[cis\text{-PtCl}(\text{NH}_3)_2(\mu\text{-4,4'}\text{-bipyridyl})\text{ZnCl}(\text{terpy})]](\text{ClO}_4)_2$  at the concentrations of 25, 50, 100, 200, and 400  $\mu\text{g}/\text{mL}$  (lanes 4-8). \* $p < 0.05$  when compared with the negative control group;  $^\ddagger p < 0.05$  when compared with the positive control group.



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In concentration range from 25 to 400  $\mu\text{g/mL}$ , the DNA-protective effect of compound  $[\{trans\text{-PtCl}(\text{NH}_3)_2(\mu\text{-4,4'-bipyridyl})\text{ZnCl}(\text{terpy})\}](\text{ClO}_4)_2$  against hydroxyl radical-induced DNA damage were dose-dependent, increasing with a higher dosage, indicating the DNA protective effect. This compound showed moderate DNA-protective effect against peroxy radical in a dose-dependent manner.

Compound  $[\{trans\text{-PtCl}(\text{NH}_3)_2(\mu\text{-pyrazine})\text{ZnCl}(\text{terpy})\}](\text{ClO}_4)_2$  showed DNA-protective effect at all tested concentrations against hydroxyl radical-induced DNA damage and had a lower ability to inhibit peroxy radical compared with hydroxyl radical inhibition.

Compound  $[\{cis\text{-PtCl}(\text{NH}_3)_2(\mu\text{-pyrazine})\text{ZnCl}(\text{terpy})\}](\text{ClO}_4)_2$  had significant dose-dependent DNA-protective effect and the same ability to inhibit peroxy as well as hydroxyl radicals.

Compound  $[\{cis\text{-PtCl}(\text{NH}_3)_2(\mu\text{-4,4'-bipyridyl})\text{ZnCl}(\text{terpy})\}](\text{ClO}_4)_2$  showed the highest DNA-protective effects at the concentrations of 400  $\mu\text{g/mL}$  against hydroxyl radical-induced DNA damage. This compound had a lower ability to inhibit peroxy radical compared with hydroxyl radical inhibition.



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## Conclusions

- i. Four novel heteronuclear complexes [*cis*- and *trans*-PtCl(NH<sub>3</sub>)<sub>2</sub>(μ-pyrazine)ZnCl(terpy)](ClO<sub>4</sub>)<sub>2</sub> and [*cis*- and *trans*-PtCl(NH<sub>3</sub>)<sub>2</sub>(μ-4,4'-bipyridyl)ZnCl(terpy)](ClO<sub>4</sub>)<sub>2</sub> were synthesized and characterized.
- ii. Two different metal centers, different in Lewis acidity and geometry in heteronuclear complex units, have influence on *in vitro* DNA damage protection activity. Generally, the complexes with cisplatin unit have better activity than with transplatin.
- iii. Type of π-acceptor bridging ligand have a greater influence on activity than geometry of Pt(II) complex unit. Thus, complexes with pyrazine as bridging ligand exerted the highest DNA protective activity.
- iv. The high DNA damage inhibiting potential of two new dinuclear complexes with pyrazine as bridging ligand could be used for further biological evaluation and development of antioxidant compounds for therapeutic applications.



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