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Cytotoxicity of novel heterometallic dinuclear complexes on colon carcinoma cell lines

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

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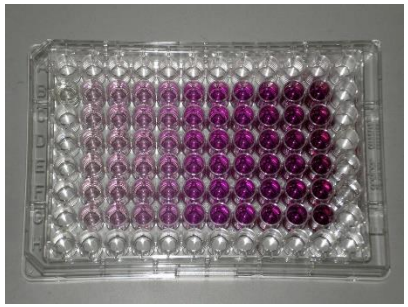
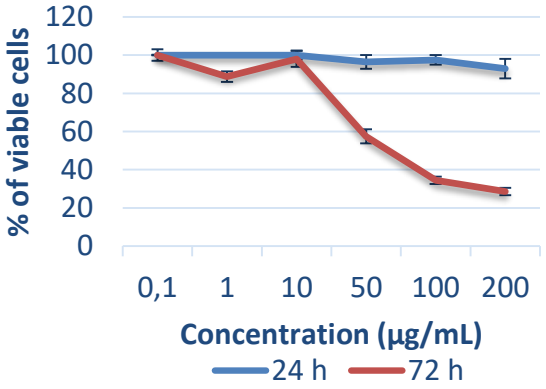
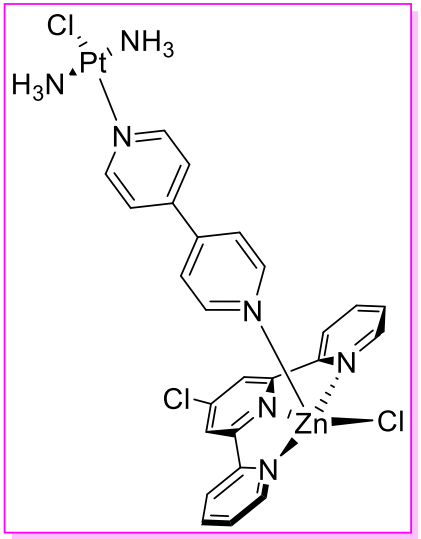
Cytotoxicity of novel heterometallic dinuclear complexes on colon carcinoma cell lines

Graphical Abstract







Abstract: **F**our new dinuclear complexes were synthesized from *cis*- and *trans*-$PtCl(NH_3)_2$ and [ZnCl(terpy-Cl)] (where terpy-Cl = 4′-chloro-2,2′:6′,2′′-terpyridine) with two different bridging ligands (4,4′-bipyridyl and pyrazine) and their cytotoxicity was evaluated on two colon carcinoma cell lines, HCT-116 and SW-480. The effect of the complexes on colon carcinoma cell lines was examined with MTT assay. On SW-480 colon cancer cells, there is no significant citotoxicity of tested complexes and IC_{50} values are higher than 200 µg/ml. HCT-116 cells are more sensitive on the treatment with these complexes. Tested complexes showed significant anticancer effect on HCT-116 colon carcinoma cell lines, but after 72 h of applied treatments. The best cytotoxic effect of all investigated complexes was pronounced after applying [{*trans*-$PtCl(NH_3)_2$(μ-4,4′-bipyridyl)ZnCl(terpy-Cl)}]$(ClO_4)_2$ complex on HCT-116 colon cancer cells after 72 h with IC_{50} = 19.52±0.78 µg/ml. The presence of the chloride in the structure of [ZnCl(terpy-Cl)] subunit of newly synthesized complexes influenced their behavior due to exchanged electronic communication between two metal centers.

Keywords: cisplatin; colon carcinoma cell lines; cytotoxic activity; terpy ligands; Zn(II) complexes.

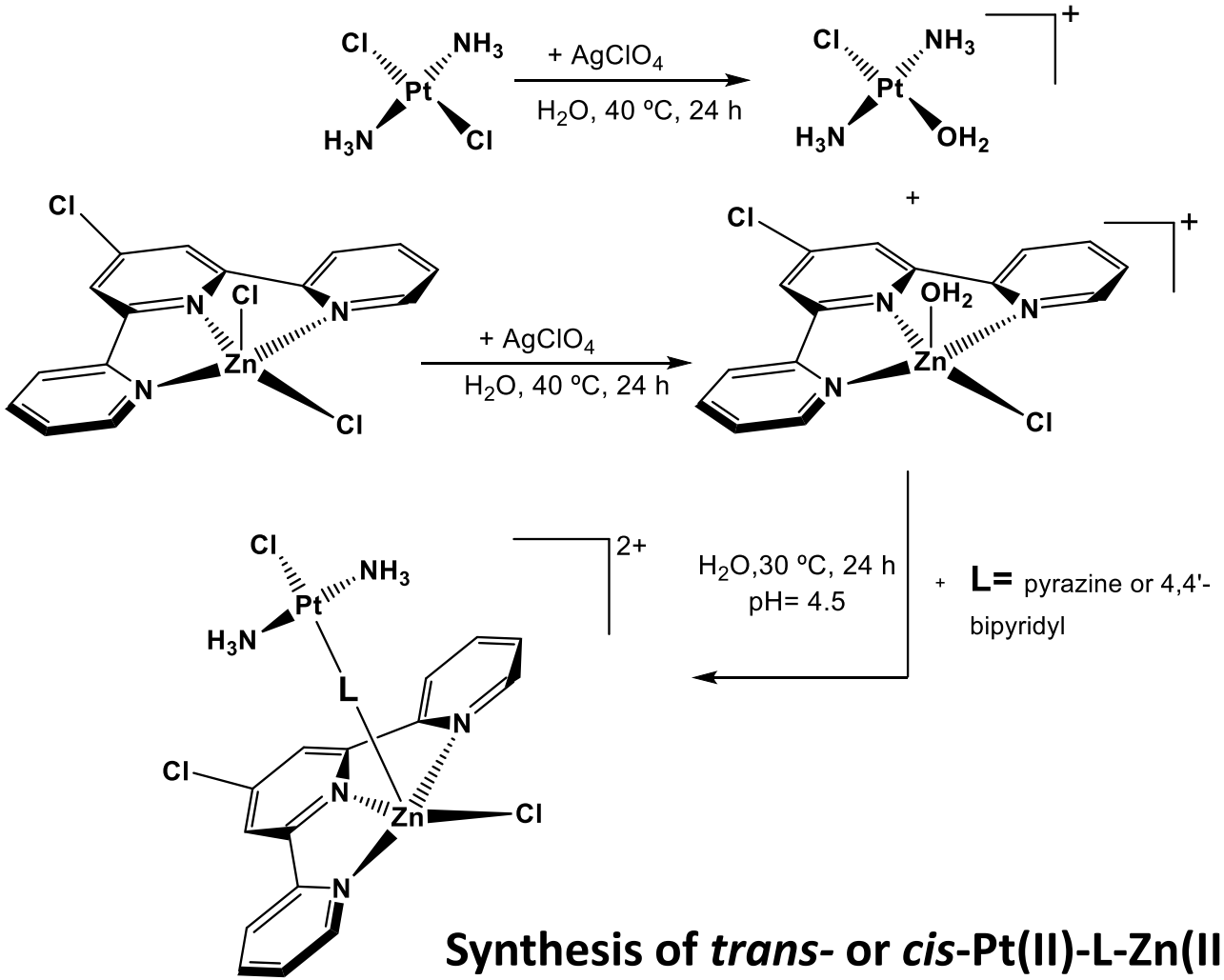
Introduction

The most applied antitumor agents based on platinum(II) metal ion, such as cisplatin, oxaliplatin or carboplatin, cause sever side-effects which limited their use, while Zn(II) ion is essential bioelement with important role in biological processes. It is already known that heterodinuclear complexes type Pt(II)-L-Zn(II) which have two different metal centers, with different Lewis acidity, geometry and kinetic characteristics, connected with π-acceptor bridging ligands, could give promising anticancer activity.

Results and discussion

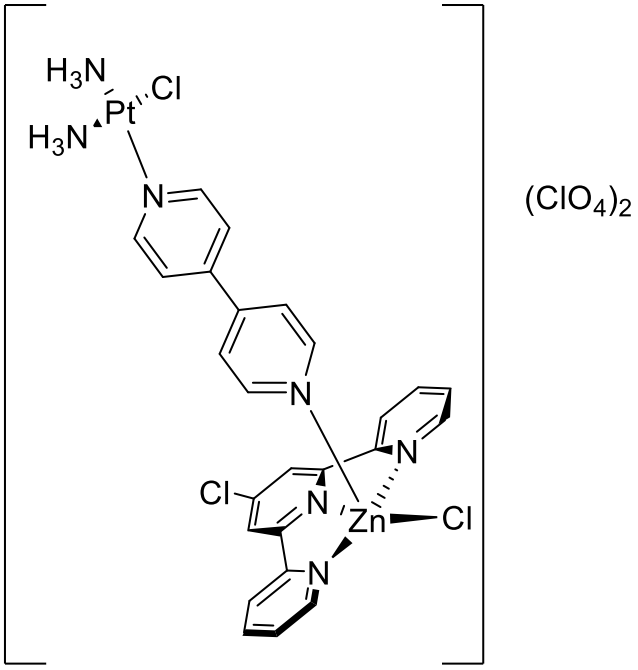
Four novel dinuclear complexes Pt(II)-L-Zn(II) were synthesized from *cis*- and *trans*-$PtCl(NH_3)_2$ and [ZnCl(terpy-Cl)] (where terpy-Cl = 4’-chloro-2,2’:6’,2’’-terpyridine) with two different bridging ligands (L = 4,4’-bipyridyl and pyrazine) in order to investigate the influence of electronic effects of chloride substituent of inert terpyridine ligand from zinc(II) center on cytotoxic properties. Synthetic procedure and cytotoxic activity of anologous complexes without substituted terpy ligand are already reported. Purity and the structure of all synthesized complexes were fully confirmed by standard methods (FT-IR and UV-Vis spectroscopy, NMR and Mass spectrometry, and molar conductivity).

Tanja V. Soldatović, Biljana Šmit, Emina M. Mrkalić, Sanja Lj. Matić, Ratomir M. Jelić, Marina Ćandić Serafinović, Nevenka Gligorijević, Milena Čavić, Sandra Aranđelović, Sanja Grgurić-Šipka, Exploring heterometallic bridged Pt(II)-Zn(II) complexes as potential antitumor agents, *Journal of Inorganic Biochemistry*, (2023) 240, 112100



Synthesis of *trans*- or *cis*-Pt(II)-L-Zn(II) complexes

Structures of the newly synthesized dinuclear complexes with 4,4′-bipyridyl bridging ligand, [{*cis*-PtCl(NH_3)$_2$(μ-4,4′-bipy)ZnCl(terpy-Cl)}](ClO_4)$_2$ (**1**) and [{*trans*-PtCl(NH_3)$_2$(μ-4,4′-bipy)ZnCl(terpy)}](ClO_4)$_2$ (**2**).



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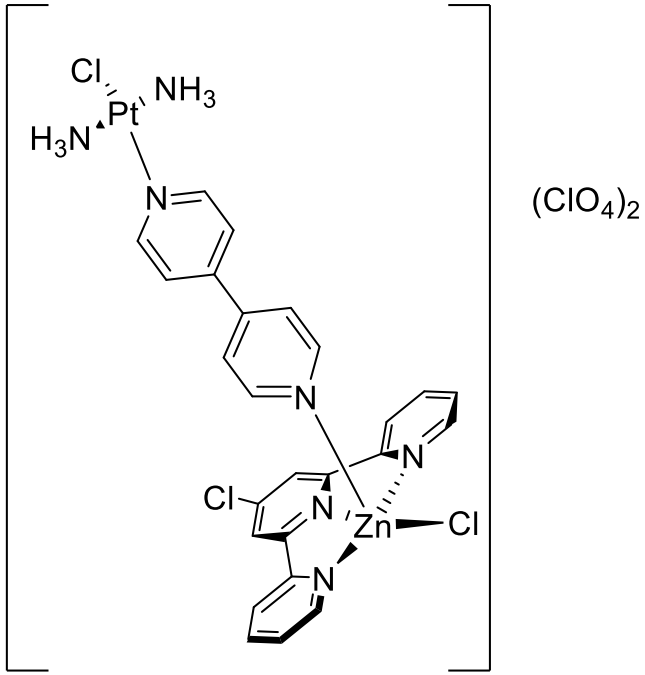
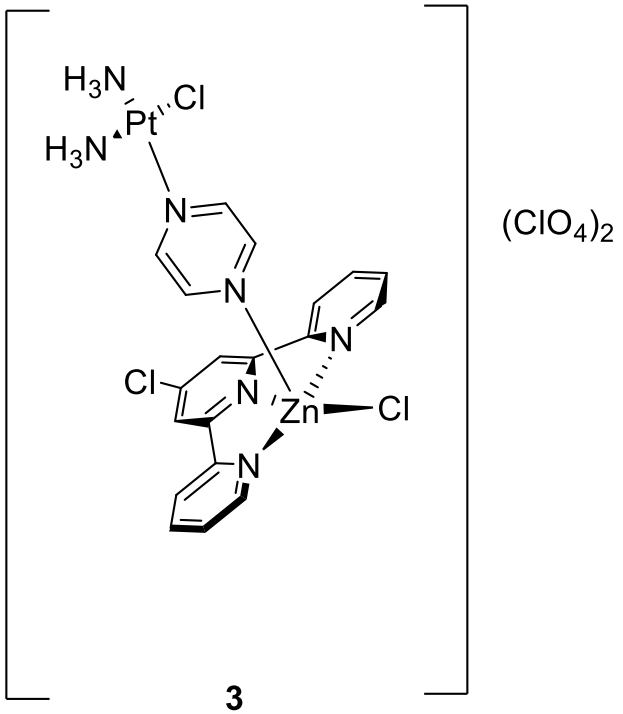


2

Structures of the newly synthesized dinuclear complexes with pyrazine bridging ligand, [{*cis*-PtCl(NH_3)$_2$(μ-4,4′-bipy)ZnCl(terpy-Cl)}](ClO_4)$_2$ (**3**) and [{*trans*-PtCl(NH_3)$_2$(μ-4,4′-bipy)ZnCl(terpy)}](ClO_4)$_2$ (**4**).



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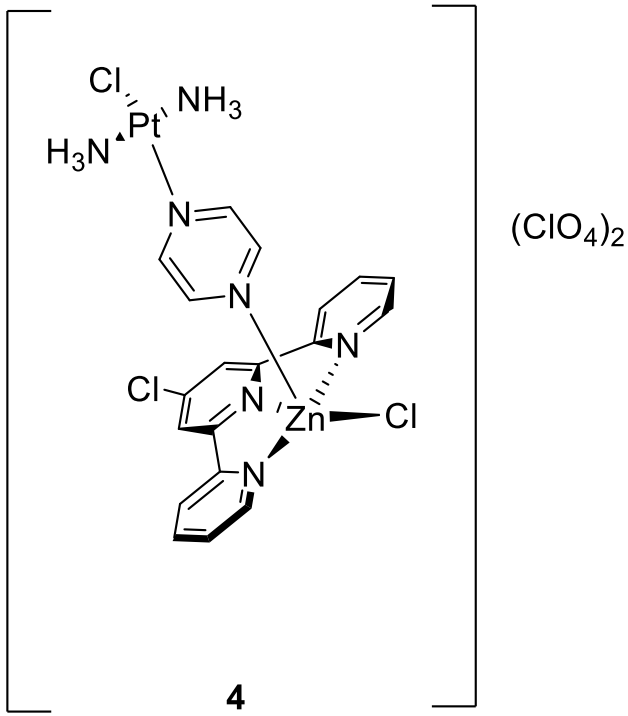
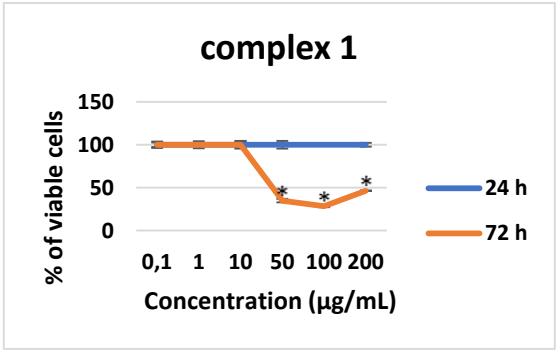
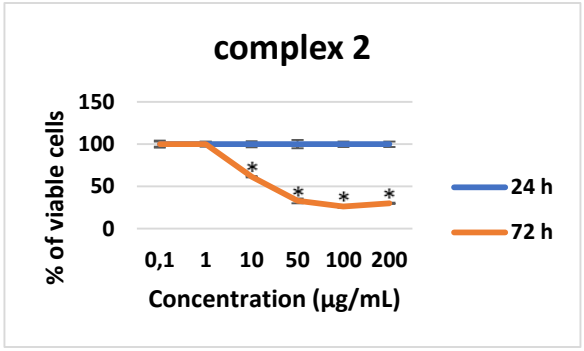
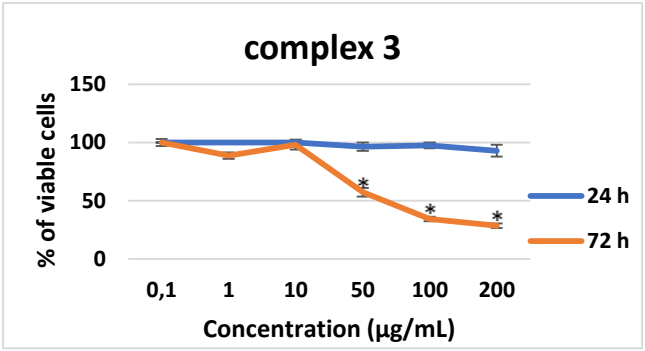


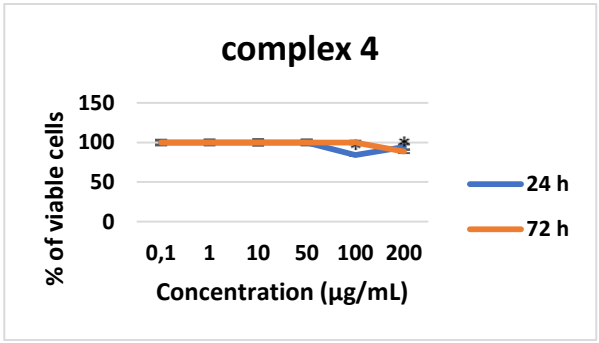
4

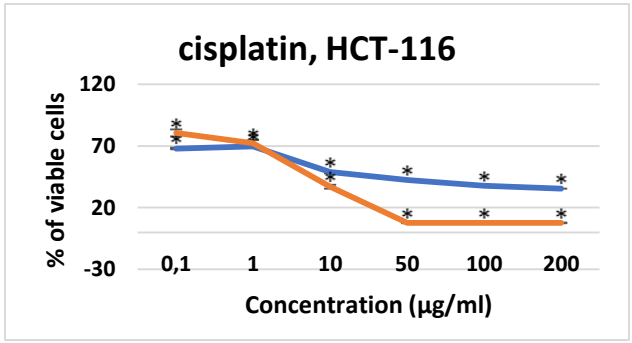
The effect of the complexes **1**-**4** and cisplatin as positive control on the viability of HCT-116 colon cancer cells, 24 and 72 h after treatment. The results are presented as the mean of three independent experiments ± standard error. * Statistically significant difference ($p < 0.05$) in relation to control values.



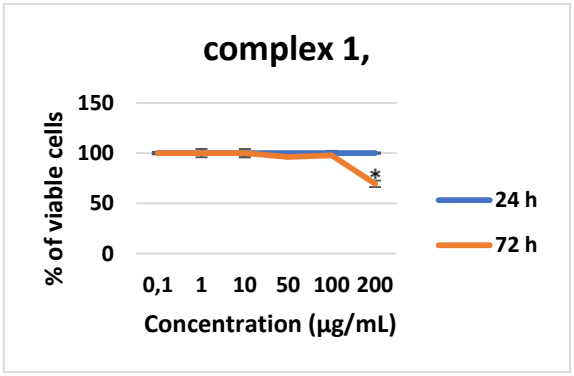


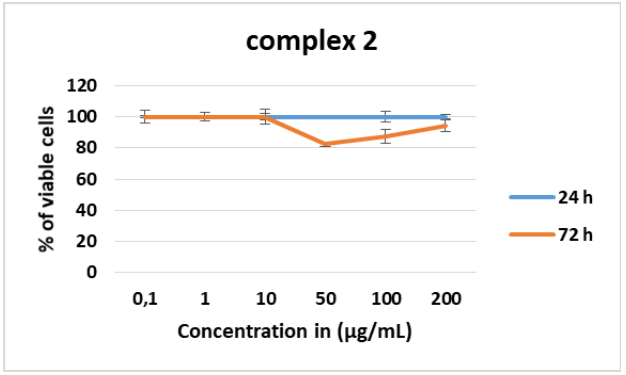


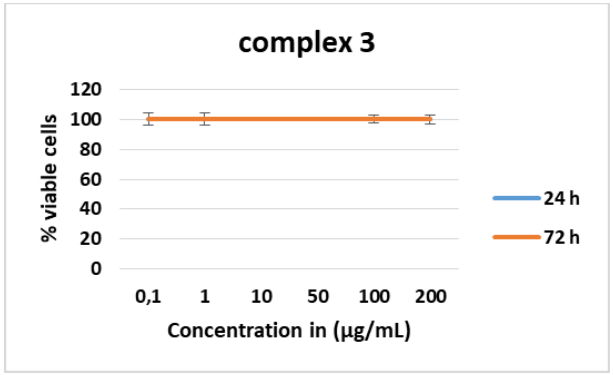


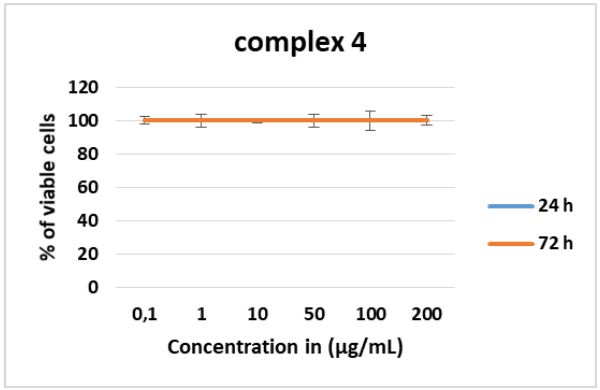


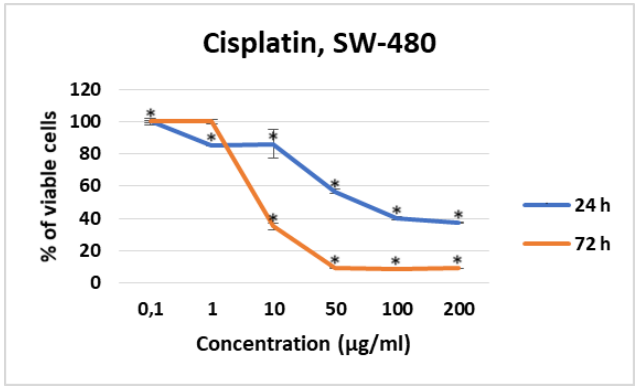
The effect of the complexes **1**-**4** and cisplatin as positive control on the viability of SW-480 colon cancer cells, 24 and 72 h after treatment. The results are presented as the mean of three independent experiments ± standard error. * Statistically significant difference ($p < 0.05$) in relation to control values.











The citotoxic effect expressed as IC_{50} values after 24 and 72 h of applied complexes **1**-**4**) on HCT-116 and SW-480 colon cancer cell lines. The results are presented as the mean of three independent experiments ± standard error. * Statistically significant difference ($p < 0.05$) in relation to control values.

IC_{50} value	HCT-116 colon cancer cell line		SW-480 colon cancer cell line	
	24 h	72 h	24 h	72 h
Complex 1	>200	43.20±0.51	>200	>200
Complex 2	>200	19.52±0.78	>200	>200
Complex 3	>200	73.31±1.95	>200	>200
Complex 4	>200	>200	>200	>200
Cisplatin	11.11±0.13	5.33±0.4	49.07±0.41	8.13±0.14

Conclusions

- Tested complexes did not show significant anticancer effect on SW-480 colon cancer cells. HCT-116 colon cancer cells are more sensitive, but only after prolonged time of 72 h.
- The best cytotoxic effect was pronounced after applying [{*trans*-$PtCl(NH_3)_2$(μ-4,4′-bipyridyl)ZnCl(terpy-Cl)}]$(ClO_4)_2$ complex on HCT-116 cells after 72 h with IC_{50} = 19.52 ± 0.78 µg/ml.
- Compared with our previous studies with complex analogues without the Cl substituent in terpy ligand, tested complexes are less active.
- The presence of Cl substituent changes the electronic communication between two metal centers and thus has influence on their behavior.

Acknowledgments

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