

## ANTIBACTERIAL ACTIVITY OF PLATINUM(II) AND PALLADIUM(II) COMPLEXES WITH SOME ALKYL ESTERS OF (S,S)-ETHYLENEDIAMINE-N,N'-DI-(2,2'-DI(4-HYDROXY)-BENZYL ACETIC ACID

Danijela Stojković<sup>1</sup>, Verica Jevtić<sup>2</sup>, Srećko Trifunović<sup>2</sup>

### Abstract

Antibiotics are used to treat many infections which are causing by different microorganisms. The vast majority of cases where antibiotics are used, the microorganisms have found a way to evade or resist the antimicrobial agent [1,2].

The work was conceived with the intention to investigate the antibacterial activity of newly synthesized ligands and complexes [3] on the selected bacterial strains with the aim to find potential synthetic preservatives.

**Keywords:** platinum(II) complexes, palladium(II) complexes, antibacterial activity

### Introduction

Bacterial resistance to antibiotics is a serious threat to the successful treatment of infectious diseases and becomes a major clinical and public health problem, leading to increased morbidity and mortality [4-6]. The synthesis and evaluation of the biological activity of the new metal-based compounds is the field of growing interest [7]. The present study was taken to investigate the antibacterial effects of newly synthesized ligands and their palladium(II) and platinum(II) complexes using the CLSI broth microdilution method. The results of the antibacterial activity of the ligands and their palladium(II) and platinum(II) complexes showed that the tested compounds have weak activity against gram negative bacteria. Recent research confirmed that Pd(II) and Pt(II) complexes showed more activity than free ligands [8].

### Material and methods

#### Test substances

The ligands and corresponding Pd(II) and Pt(II) complexes that were tested for their *in vitro* antimicrobial activity: edtyr-etil·2HCl·2H<sub>2</sub>O (**L1**); edtyr-propil·2HCl·2H<sub>2</sub>O (**L2**); edtyr-butyl·2HCl·2H<sub>2</sub>O (**L3**); edtyr-pentil·2HCl·2H<sub>2</sub>O (**L4**) [9]. [PdCl<sub>2</sub>(edtyr-etil)] (**C1**); [PdCl<sub>2</sub>(edtyr-propil)] (**C2**); [PdCl<sub>2</sub>(edtyr-butyl)] (**C3**); [PdCl<sub>2</sub>(edtyr-pentil)] (**C4**) [3]; [PtCl<sub>2</sub>(edtyr-etil)] (**DS1**); [PtCl<sub>2</sub>(edtyr-propil)] (**DS2**); [PtCl<sub>2</sub>(edtyr-butyl)] (**DS3**); [PtCl<sub>2</sub>(edtyr-pentil)] (**DS4**); Each tested substance (3 mg)

<sup>1</sup>University of Kragujevac, Faculty of Agronomy in Čačak, Cara Dušana 34, Čačak, Srbija (danijela.stojkovic@kg.ac.rs);

<sup>2</sup>University of Kragujevac, Faculty of Science in Kragujevac, Radoja Domanovića 12, Kragujevac, Srbija

was dissolved in 150 µL DMSO (Dimethyl Sulfoxide) and then diluted with 1350 µL of normal saline to the final concentration of stock solution at 2000 mg/mL (10% DMSO).

### Microdilution method

Antibacterial activity was tested using the broth microdilution method according to the CLSI Standards [10] and minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were determined. Direct colony suspensions were prepared using overnight broth cultures and suspensions were adjusted to 0.5 McFarland turbidity standard ( $1 \times 10^8$  CFU/mL). A two-fold serial dilution of tested compounds was prepared in a 96 well microtiter plate (range 1000-15.625 µg/mL) in inoculated nutrient broth adjusted to the final concentration of  $5.0 \times 10^5$  CFU/mL for each bacterial strain. The plates were covered with a plastic lid and incubated at 37°C for 18-24 h. Ceftriaxone and vancomycin (Galenika AD, Belgrade) served as a positive control, while the solvent was used as a negative control. MIC was defined as the lowest concentration of tested compounds inhibiting the visible growth of each tested organism. To determine MBC broth was taken from all wells without visible growth as well as from the wells with the highest concentration of substances that still showed visible growth and inoculated onto Mueller-Hinton agar plates (Torlak, Beograd). At the end of the incubation period (24h/37°C) the lowest concentration with no growth (no colony) was defined as minimum bactericidal concentration.

### Results and Discussion

The results of the antibacterial activity of the ligands and their palladium(II) and platinum(II) complexes are shown in *Table 1*.

**Table 1.** Antibacterial activity (µg/mL) of tested ligands, corresponding palladium(II) and platinum(II) complexes

Ligands and corresponding complexes		BC		EC		SA		PA		EF		SE
		ref	cli	ref	cli	ref	cli	ref	cli	ref	cli	ref
<b>L1</b>	MIC	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	500	>10 <sup>3</sup>	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
<b>C1</b>	MIC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
<b>DS1</b>	MIC	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
<b>L2</b>	MIC	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	500	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
<b>C2</b>	MIC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
<b>DS2</b>	MIC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	500	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>

<b>L3</b>	MIC	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
<b>C3</b>	MIC	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	125	10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	500	>10 <sup>3</sup>
<b>DS3</b>	MIC	10 <sup>3</sup>	500	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	500	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>
<b>L4</b>	MIC	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	10 <sup>3</sup>	500	>10 <sup>3</sup>
	MBC	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	500	>10 <sup>3</sup>
<b>C4</b>	MIC	103	103	103	103	103	103	103	103	103	500	>103
	MBC	>103	>103	>103	>103	103	>103	>103	>103	>103	>103	>103
<b>DS4</b>	MIC	103	500	>103	>103	103	103	500	>103	>103	>103	>103
	MBC	>103	>103	>103	>103	103	>103	>103	>103	>103	>103	>103

**BC** - *Bacillus cereus* ATCC 10876 and clinical strain, **EC** - *Escherichia coli* ATCC 25922 and clinical strain, **SA** - *Staphylococcus aureus* ATCC 25923 and clinical strain, **PA** - *Pseudomonas aeruginosa* ATCC 27853 and clinical strain, **EF** - *Enterococcus faecalis* ATCC 29212 and clinical strain, **SE** - *Salmonella enterica* subspecies *enterica* serovar *enteritidis* ATCC 13076.

### Conclusions

The antibacterial activity results showed that all of the ligands and their corresponding complexes have weak activity against gram-negative bacteria. Generally, the antibacterial activities of all of the complexes are greater than those of the ligands.

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### References

- [1] Powledge T.M., New Antibiotics-Resistance Is Futile. PLoS Biol. 2(2) (2004) e53. doi:10.1371/journal.pbio.0020053
- [2] CDC. Reported Tuberculosis in the United States, 2008 (<http://www.cdc.gov/tb>).
- [3] Moellering R.C., Graybill J.R., McGowan J.E., Corey L., Antimicrobial resistance prevention initiative an update: proceedings of an expert panel on resistance, Am. J. Med. 120 (2007) S4-25; quiz S26-8.
- [4] Spellberg B., Guidos R., Gilbert D., J. Bradley, Boucher H.W. Scheld W.M., Bartlett J.G., Edwards J., The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America, Clin. Infect. Dis. 46 (2008) 155-164.
- [5] Taiwo S.S., Antibiotic-resistant bugs in the 21st century: A public health challenge. World J. Clin. Infect. Dis. 1(1) (2011) 11-16.

- [6] Vasić G.P., Glodjović V.V., Radojević I.D., Stefanović O.D., Čomic L.J.R., Djinović V.M., S.R. Trifunović, Stereospecific ligands and their complexes. V. Synthesis, characterization and antimicrobial activity of palladium(II) complexes with some alkyl esters of (*S,S*)-ethylenediamine-*N,N'*-di-2-propanoic acid, *Inorganica Chimica Acta* 363 (2010) 3606-3610.
- [7] Samota M.K., Seth G., Synthesis, characterization, and antimicrobial activity of palladium(II) and platinum(II) complexes with 2-substituted benzoxazole ligands. *Heteroatom Chem.* 21(1), (2010) 44-50.
- [8] Schoenberg L.N., Cooke D.W., Liu C. F., *Inorg. Chem.* 7 (1968) 2386.
- [9] Stojković D., Jevtić V., Radić G., Todorović D., Petrović M., Zarić M., Nikolić I., Baskić D., Trifunović S., Stereospecific ligands and their complexes. XXII. Synthesis and antitumor activity of palladium(II) complexes with some esters of (*S,S*)-ethylenediamine-*N,N'*-di-(2,2'-di(4-hydroxy)-benzyl-acetyl) acid, *Journal of Inorganic Biochemistry* 143 (2015) 111-116.
- [10] Clinical and Laboratory Standards Institute 2010. Performance standards for antimicrobial susceptibility testing; 20th informational supplement (M100-S20). Clinical and Laboratory Standards Institute, Wayne, PA.

## ANTIBAKTERIJSKA AKTIVNOST PLATINA(II) I PALADIJUM(II) KOMPLEKSA SA ALKIL ESTRIMA (*S,S*)-ETILENDIAMIN-*N,N'*-DI-(2,2'-DI(4-HIDROKSI)-BENZIL SIRČETNE KISELINE

*Danijela Stojković<sup>1</sup>, Verica Jevtić<sup>2</sup>, Srećko Trifunović<sup>2</sup>*

### Izvod

Antibakterijska sredstva se koriste u lečenju mnogih infekcija koje uzrokuju različiti mikroorganizmi.

U najvećem broju slučajeva, u kojima se koriste antibakterijska sredstva, mikroorganizmi su pronašli način da se odupru ili izbegnu antimikrobni agens [1,2]. Rad je koncipiran sa namerom da ispita antibakterijsku aktivnost novosintetisanih i liganada i kompleksa [9] na odabranim bakterijskim sojevima u cilju pronalazjenja novih potencijalnih sintetičkih konzervanasa.

**Ključne reči:** platina(II) kompleksi, paladijum(II) kompleksi, antibakterijska aktivnost.

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<sup>1</sup>Univerzitet u Kragujevcu, Agronomski fakultet u Čačku, Cara Dušana 34, Čačak, Srbija (danijela.stojkovic@kg.ac.rs)

<sup>2</sup>Univerzitet u Kragujevcu, Prirodno-matematički fakultet u Kragujevcu, Radoja Domanovića 12, Kragujevac, Srbija