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Antibacterial and Antibiofilm Screening of New Platinum(IV) Complexes with some S-Alkyl Derivatives of Thiosalicylic Acid

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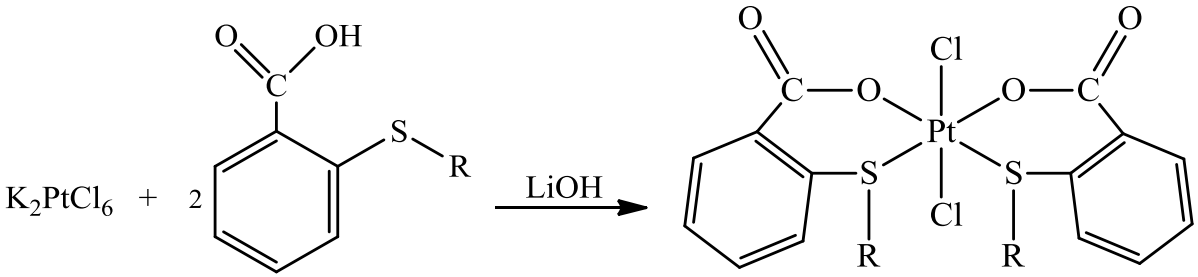

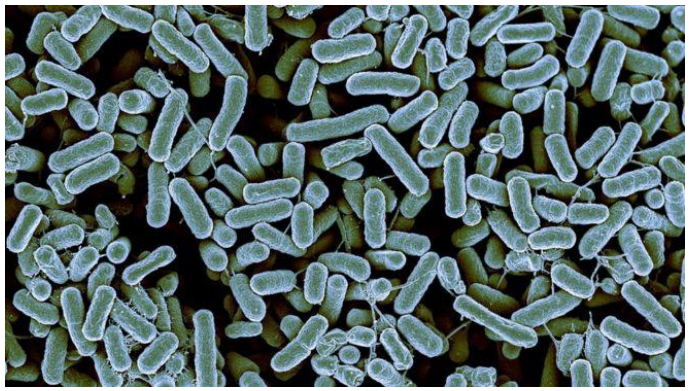

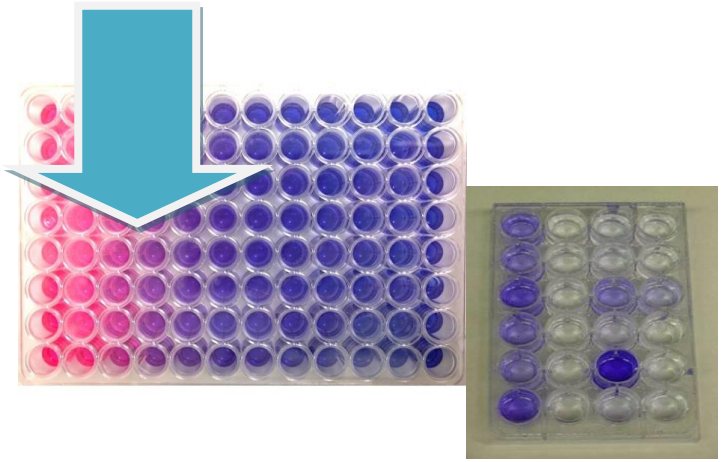

Abstract: This investigation showed influence of 5 new Pt(IV) complexes on 16 strains of bacteria. Antibacterial activity was tested using microdilution method with resazurin while antibiofilm activity was observed by tissue culture plate method and antibiotic doxycycline was used as positive control. The results were expressed as minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and biofilm inhibitory concentration (BIC). The complexes were labeled from C1 to C5. The best result on Gram positive bacteria was obtained with C1 and MIC on *Staphylococcus aureus* ATCC 25923 was <7.81 µg/ml. *Bifidobacterium animalis subsp. lactis* (probiotic) was sensitive to C2 (MIC at 15.625 µg/ml). The best sensitivity on Gram negative bacteria was observed on *Escherichia coli* ATCC 25922 with C1, C2, C3 and C4, on *Proteus mirabilis* ATCC 12453 with C1, and on *Pseudomonas aeruginosa* with C2, C3 and C5 (all MICs at 250 µg/ml). The tested complexes were more efficient as antibiofilm agents and the best results were obtained with C2 acting against *S. aureus* and *S. aureus* ATCC 25923 biofilm. In conclusion, we noticed that the tested compounds exhibited promising properties as antibacterial agents and antibiofilm agents.

Keywords: platinum(IV) complex; antibacterial activity; antibiofilm

Introduction

The interest in determining the influence of new metal complexes on microorganisms is increasing due to the growing pathogenic resistance. New synthesized Pt(IV) complexes were labeled as: C1 for Pt(S-bz-thiosal)$_3$, C2 for Pt(S-met-thiosal)$_3$, C3 for Pt(S-et-thiosal)$_3$, C4 for Pt(S-pr-thiosal)$_3$ and C5 for Pt(S-bu-thiosal)$_3$. Our goal was *in vitro* testing of those complexes, in order to obtain the antimicrobial results and for the first time the antibiofilm results of any Pt(IV) complexes.

Investigations of other Pt complexes in microbiology have been conducted, showing wide influence on microorganisms but being more or less effective. It includes bimetallic complexes (Al-Hasani, 2007), Pt complexes as polymeric nanoparticles (Elhusseiny and Hassan, 2013), different polymers with Pt(IV) (Nartop et al., 2013), Pt(IV) chelate (Hegazy, 2012), Pt(IV) dithiocarbamate complexes (Manav et al., 2006), thiodiamines with Pt(IV) (Mishra and Kaushik, 2007), etc.

The synthesis of complexes

S-benzyl derivative of thiosalicylic acid (for C1 and for: C2 S-methyl, C3 S-ethyl, C4 S-propyl, C5 S-butyl) in amount of 0.6 mmol was slowly added to the solution of 0.2 mmol (0.1 g) potassium-hexachloroplatinum(IV) with 10 ml of distilled water. The reaction mixture was heated on a water bath with stirring for 3 h. During this period, small portions from a solution of LiOH (0.6 mmol with 10 ml of distilled water) were added. The precipitate of the complex was separated by filtration, rinsed with distilled water and dried in air.

C1 → $M(PtC_{42}H_{33}S_3O_6) = 924{,}784\ g \cdot mol^{-1}$
C2 → $M(PtC_{24}H_{21}S_3O_6) = 696{,}368\ g \cdot mol^{-1}$
C3 → $M(PtC_{27}H_{27}S_3O_6) = 738{,}586\ g \cdot mol^{-1}$
C4 → $M(PtC_{30}H_{33}S_3O_6) = 780{,}664\ g \cdot mol^{-1}$
C5 → $M(PtC_{33}H_{39}S_3O_6) = 822{,}742\ g \cdot mol^{-1}$

Results and discussion

Antibacterial activity

The test results of *in vitro* antimicrobial activity of Pt(IV) complexes are presented in Tables 1 and 2, showing only the strains that exhibited sensitivity. The detected values were in range from less than 7.81 up to more than 1000 μg/ml. For comparison, MIC and MBC values of doxycycline are also listed. Gram positive bacteria showed higher sensitivity than Gram negative bacteria.

Significant sensitivity, between Gram positive bacteria in the presence of Pt(IV) complexes, showed *Bifidobacterium animalis subsp. lactis*, *Bacillus subtilis*, *Staphylococcus aureus* and *Staphylococcus aureus* ATCC 25923. The best result was obtained with C1 and MIC on *S. aureus* ATCC 25923 was <7.81 μg/ml. *B. animalis subsp. lactis* (probiotic) showed sensitivity with C1 (MIC at 62.5 μg/ml) and better with C2 (MIC at 15.625 μg/ml). MIC for the Gram negative bacteria was in the range from 250 to >1000 μg/ml. The best sensitivity showed *Escherichia coli* ATCC 25922 with C1, C2, C3 and C4, *Proteus mirabilis* ATCC 12453 with C1 and *Pseudomonas aeruginosa* with C2, C3 and C5 (all MICs at 250 μg/ml).

Table 1. Antibacterial activity of Pt(IV) complexes (C1, C2, C3), MIC values (μg/ml) – means inhibitory activity, MBC values (μg/ml) – means bactericidal activity.

Species	C1		C2		C3	
	MIC	MBC	MIC	MBC	MIC	MBC
Bifidobac. animalis subsp. lactis	62.5	125	125	250	125	250
Bacillus subtilis	62.5	500	250	500	31.25	500
Staphylococcus aureus	62.5	125	62.5	500	250	500
S. aureus ATCC 25923	<7.81	62.5	125	250	125	500
Escherichia coli ATCC 25922	250	500	250	500	250	500
Proteus mirabilis ATTC 12453	250	500	500	500	500	500
Pseudomonas aeruginosa	500	>1000	250	1000	250	1000

Comparing the results obtained for the Pt(IV) complexes with the results of corresponding ligands from which they were synthetized (Radić et al., 2012) it can be concluded that these complexes had better antibacterial activity than the ligands. Hegazy and Gaafar (2012) tested synthetized Pt(IV) complex on 10 pathogenic bacteria and had high efficiency against all the strains, including *Salmonella sp.*, *S. aureus* and *B. subtilis*, while the Pt(IV) dithiocarbamate complexes investigated by Manav et al. (2006) were less active against *E. coli*, *B. subtilis* and *P. aeruginosa*.

Table 2. Antibacterial activity of Pt(IV) complexes (C4, C5) and positive control (doxycycline), MIC values (μg/ml) – means inhibitory activity, MBC values (μg/ml) – means bactericidal activity.

Species	C4		C5		Doxycycline	
	MIC	MBC	MIC	MBC	MIC	MBC
Bifidobac. animalis subsp. lactis	250	250	250	250	31.25	62.5
Bacillus subtilis	62.5	500	62.5	500	0.11	1.95
Staphylococcus aureus	250	500	125	500	0.45	7.81
S. aureus ATCC 25923	125	250	125	250	0.22	3.75
Escherichia coli ATCC 25922	250	500	500	500	15.63	31.25
Proteus mirabilis ATTC 12453	1000	1000	500	1000	15.63	62.5
Pseudomonas aeruginosa	500	>1000	250	1000	250	1000

Table 3. Antibiofilm activity of Pt(IV) complexes C1 to C5 and positive control (doxycycline), BIC values (μg/ml) – means biofilm inhibitory concentration, nt – not tested.

Species	C1	C2	C3	C4	C5	Doxycycline
	BIC					
Staphylococcus aureus	250	62.5	125	500	125	250
Staphylococcus aureus ATCC 25923	500	62.5	1000	250	1000	250
Proteus mirabilis ATCC 12453	1000	>1000	1000	nt	1000	nt
Pseudomonas aeruginosa	1000	1000	1000	1000	1000	2000

Antibiofilm activity

The test was performed against 4 strains of bacteria to obtain the *in vitro* antibiofilm activity of Pt(IV) complexes presented in Table 3. The best results showed C2 acting against *S. aureus* and *S. aureus* ATCC 25923 biofilm and it was noticed that obtained values were lower than antibiotic values in this first antibiofilm testing of this kind of complexes.

References

Al-Hasani AMR. Preparation, structural and antimicrobial studies of a new bimetallic complexes involving a new schiff and mannich bases. *Journal of Al-Nahrain University* 10.2 (2007): 39-49.

Elhusseiny AF, Hassan HHAM. Antimicrobial and antitumor activity of platinum and palladium complexes of novel spherical aramides nanoparticles containing flexibilizing linkages: Structure–property relationship. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 103 (2013): 232-245.

Hegazy WH, Gaafar M. Synthesis, characterization and antibacterial activities of new Pd (II) and Pt (IV) complexes of some unsymmetrical tetradentate schiff bases. *American Chemical Science Journal* 2.3 (2012): 86.

Hegazy WH. Synthesis of organometallic-based biologically active compounds: In vitro antibacterial and antifungal of asymmetric ferrocene-derived schiff-bases chelates. *International Research Journal of Pure and Applied Chemistry* 2.3 (2012): 170.

Manav N, Mishra AK, Kaushik NK. In vitro antitumour and antibacterial studies of some Pt (IV) dithiocarbamate complexes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 65.1 (2006): 32-35.

Mishra AK, Kaushik NK. Synthesis, characterization, cytotoxicity, antibacterial and antifungal evaluation of some new platinum (IV) and palladium (II) complexes of thiodiamines. *European Journal of Medicinal Chemistry* 42.10 (2007): 1239-1246.

Nartop D, Sari N, Ögütçü H. Pt (IV) complexes with polystrene-bound schiff bases as antimicrobial agent: Synthesis and characterization. *Proceedings of World Academy of Science, Engineering and Technology*. No. 78. World Academy of Science, Engineering and Technology (WASET), 2013.

Radić G, Gloďović V, Radojević I, Stefanović O, Čomić Lj, Ratković Z, Valkonen A, Rissanen K, Trifunović S. Synthesis, characterization and antimicrobial activity of palladium(II) complexes with some alkyl derivates of thiosalicylic acids. Crystal structure of bis(S-benzyl-thiosalicylate)-palladium(II) complex, [Pd(S-bz-thiosal)2]. *Polyhedron* 31.1 (2012): 69-76.

Conclusions

The Pt(IV) complexes have showed significant activity against the tested bacteria. The best results were antibacterial and antibiofilm activity against *S. aureus* and *S. aureus* ATCC 25923. Since these bacteria can cause different medical problems, Pt(IV) complexes should be considered for more examinations.

Acknowledgments

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