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## STUDY OF THE ANTIMICROBIAL ACTIVITY OF SOME FERROCENE DERIVATIVES

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### Introduction

Ferrocene derivatives represent an important class of organometallic compounds, having a wide range of biological activities, such as antimicrobial activity and antioxidant activity.

Given the need for new compounds with antimicrobial activity, we directed our researches in the direction of ferrocene derivatives which have heterocyclic molecules as synthons. The antimicrobial activity of these compounds was tested on bacterial biological models.

### Materials and methods

The antimicrobial activity of the newly synthesized compounds was tested on Gram negative and Gram positive bacterial strains, such as *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 25922) and also *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (ATCC 6538). The qualitative testing of antimicrobial activity of precursors and ferrocene derivatives was performed by a method adapted to the disk-diffusimetric one. Briefly, bacterial strains in liquid medium (Mueller Hinton) were incubated in presence of a wide range of precursors (ferrocene-carbaldehyde-Fe-CO, 4-aminoantipyrene-4-AAP, 2-aminopyridine-2-AP) and ferrocene-carbaldehyde derivatives (FeCO-AAP and Fe-AP) concentrations (0-10 mg/mL), prepared in dimethylsulfoxide (DMSO), and the bacterial minimum inhibitory concentration (MIC) was detected by a serial microdilutions method in 96 wells plates. MIC is the smallest amount of the compound solution capable to initiate bacterial growth inhibition.

### Results and conclusions

The objectives we pursued were:

- qualitative screening of the antimicrobial activity of the synthesized derivatives

- quantitative determination of antimicrobial activity
- the study of the influence of the solutions of ferrocene derivatives on the development of microbial biofilms on inert substrate.

The quantitative determinations revealed that, overall, tested samples showed a good antimicrobial activity. The compounds had a good activity against Gram positive strains *Enterococcus faecalis* and *Staphylococcus aureus* with MIC values between 0.156 – 1.25 mg/mL (Table 1).

Moreover, quantitative determinations revealed that precursors and ferrocene derivatives exerted satisfactory inhibitory effects against Gram negative strains such as *Pseudomonas aeruginosa* and *Escherichia coli*, with MIC values between 0.625 – 2.5 mg/mL (Table 1).

**Table 1.** MIC values (mg/mL) tested on bacterial strains

| Test compound | <i>Pseudomonas aeruginosa</i> 27853 | <i>Escherichia coli</i> 25922 | <i>Enterococcus faecalis</i> 29212 | <i>Staphylococcus aureus</i> 6538 |
|---------------|-------------------------------------|-------------------------------|------------------------------------|-----------------------------------|
| Fe-CO         | 1.25                                | 1.25                          | 1.25                               | 0.156                             |
| 4-AAP         | 0.625                               | 1.25                          | 1.25                               | 1.25                              |
| 2-AP          | 0.625                               | 1.25                          | 1.25                               | 0.625                             |
| FeCO-AAP      | 2.5                                 | 2.5                           | 1.25                               | 0.625                             |
| Fe-AP         | 1.25                                | 2.5                           | 1.25                               | 0.312                             |
| DMSO          | 6.25 %                              | 12.50 %                       | 12.50 %                            | 12.50 %                           |

Adhesion to a substrate is the initial and essential stage of the microbial biofilm formation. One of the most important consequences of biofilm formation is the increased resistance of cells belonging to the biofilm. The results showed that the inhibitory effect of the tested compounds on bacterial biofilms was manifested at concentrations between 0.156 and > 2.5 mg/mL. Microbial biofilms produced by *Pseudomonas aeruginosa* and *Staphylococcus aureus* showed a higher sensitivity to the tested compounds compared to *Escherichia coli* and *Enterococcus faecalis* (Table 2).

**Table 2.** MIC values (mg/mL) tested on bacterial biofilms

| Test compound | <i>Pseudomonas aeruginosa</i> 27853 | <i>Escherichia coli</i> 25922 | <i>Enterococcus faecalis</i> 29212 | <i>Staphylococcus aureus</i> 6538 |
|---------------|-------------------------------------|-------------------------------|------------------------------------|-----------------------------------|
| Fe-CO         | 1.25                                | 1.25                          | 1.25                               | 0.156                             |
| 4-AAP         | 0.625                               | 1.25                          | 1.25                               | 2.5                               |
| 2-AP          | 0.625                               | 1.25                          | 1.25                               | 2.5                               |
| FeCO-AAP      | 0.625                               | 1.25                          | 1.25                               | 0.625                             |
| Fe-AP         | 10                                  | 10                            | 10                                 | 0.312                             |
| DMSO          | 6.25 %                              | 12.50 %                       | 12.50 %                            | 25 %                              |

In conclusion, Schiff bases derived from Fe-CO and 4-AAP and 2-AP had the best antimicrobial and antibiofilm activity inhibition based on *Staphylococcus aureus*.