

Synthesis and Determination of Antibacterial Activity of Jacaranone and Synthetic Analogs

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Abstract

Natural product jacaranone, **1**, and five more analog derivatives were synthesized and its antibacterial activity against Gram-positive and Gram-negative microorganisms was tested. One of these derivatives, **5**, was more active than the natural product, and exhibited a bactericidal effect against Gram-positive and Gram-negative bacteria.

Keywords: Jacaranone, Jacaranone Antimicrobial Activity, Jacaranone Synthetic Analogs

1. Introduction

The appearance of antibiotics represented a very important weapon in fighting bacterial infections, their contribution for human health has no question. Nevertheless, because of the emergence of drug resistant bacteria or because of the production of toxic reactions, these have become less and less effective. Actually, the multiple antibiotic resistances among pathogenic bacteria represents a risk for human health. Bacterial infections due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi* and even *Escherichia coli* are a major source of morbidity and mortality not just in hospitals but also among community [1].

Due to the failure of available antimicrobials to treat infectious diseases, actual research is focussed on the investigation and development of new products as source of new bioactive molecules [2]. Research for synthetic antimicrobial drugs has increased lately, mainly because their structures are different from known molecules and therefore their action mode may differ from known antibiotics [1].

Many natural products are a source of pharmaceutical drugs by themselves, or as an inspirational model for the synthesis of even more active analogs. In 1976 Farnsworth *et al* reported [3] that methanolic extracts from the plant *Jacaranda caucana* (Bignoniaceae) showed activity against P-388 lymphocytic leukemia. They isolated and identified the compound responsible for this activity: a benzoquinoid named as jacaranone, **1**. Since then, this phytoquinoid has been isolated from many species of flowering plants of the families Asteraceae (or

Compositae) [4-10] and Bignoniaceae [11-14], both widely distributed in the tropical and subtropical areas of the world [2]. Jacaranone, **1**, has also been isolated from plants of the Pentaphylacaceae family [15,16] and from the algae *Delesseria sanguinea* (Delesseriaceae) [17].

Some jacaranone structurally-related derivatives have also been isolated from some plants of the families Asteraceae [18-20], Bignoniaceae [21,22], Acanthaceae [23], Oleaceae [24] and Stilbaceae [25]. Because of the widespread occurrence of jacaranone and analogs in plants, some authors have suggested that, these quinols may not be specific secondary metabolites, but they may be involved in the primary metabolism related with the prephenic-shikimic-chorismic acids route as evidenced by the close structural similarity of these products with prephenic acid [25].

Interestingly, some brominated jacaranone derivatives, possessing antibacterial activity, have been isolated from the marine opisthobranch gastropod mollusk *Tyrodina fungina* (Tyrodinidae) [26] and from the marine sponge of the genus *Verongia* (Aplysinidae) [27].

Many species of the genus *Jacaranda*, in the family Bignoniaceae, have been ethnobotanically used in order to control infectious diseases [28]. For example, leaves of *Jacaranda oxyphylla* have been used in traditional medicine to treat microbial infections [22]. Jacaranone, **1**, is the most important biologically active compound isolated from this genus.

Ternstroemia pringlei, from the family Pentaphylacaceae, is one of the most used medicinal plants in Mexico, and has been popularly employed as a tranquilizer and for the treatment of insomnia. The sedative compound was established as jacaranone, **1** [15].

Jacaranone, **1**, itself, has been reported to have a broad biological activity: antitumor activity and induces

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apoptosis in murine melanoma cells [29], moderate activity against leishmaniasis [30], cytotoxic activity against prostate carcinoma cell lines [31], antibacterial activity [32], and anti-malarial and anti-trypanosomal activity [33].

The aim of this study was to synthesize jacaranone, **1**, and several synthetic analogs (**2-6**), to evaluate its antibacterial activity and determine the minimal inhibitory concentration (MIC) of these compounds, against some common food spoilage and pathogenic microorganisms including *Staphylococcus aureus*, *Lactobacillus plantarum*, *Leuconostoc mesenteroides*, *Listeria monocytogenes*, *Escherichia coli*, *Salmonella enteritidis*, *Pseudomonas aeruginosa* and *Candida albicans*.

Detection of antimicrobial activity of new products may be tested either by bioautographic, diffusion and dilution methods. Of these, first two methods give qualitative results, instead, dilution methods are considered as quantitative, since minimal inhibitory concentration may be determined.

2. Materials and Methods

2.1. Synthesis. General Information

All glassware and syringes were dried in an oven overnight at 140° C and flushed with nitrogen immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All reactions were carried out under a positive pressure of nitrogen. Nitrogen was passed through a Drierite gas-drying unit. Diethyl ether and tetrahydrofuran were refluxed and freshly distilled from sodium and potassium/benzophenone ketyl respectively, under nitrogen atmosphere. Diisopropylamine was distilled from sodium, under nitrogen, immediately prior to use. *n*-Butyllithium was titrated with 2-butanol and 1,10-phenanthroline was used as indicator. ¹H-NMR and ¹³C-NMR spectra were recorded on a 400 MHz Bruker spectrometer. High resolution mass were measured on a Waters Synapt HMD S G1, Q-TOF. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000.

2.1.1. Synthesis of jacaranone derivatives

In a three necked 50 mL round bottom flask, equipped with a magnetic stirring bar, and an addition funnel with pressure-equalizing arm, capped with a rubber septum, was added diisopropylamine (0,5 mL, 3.7 mmol) and THF (10 mL) and cooled to -30° C. A solution of *n*-BuLi in hexanes was added dropwise and the solution stirred for 20 minutes. The temperature was lowered to -78° C and the corresponding acetate (3.7 mmol) in THF (6 mL) was added dropwise through the addition funnel and the resulting solution stirred for 40 additional minutes at this temperature.

In a second assembly a three necked 250 mL round-bottom flask, equipped with a magnetic stirring bar and a dry-ice jacketed addition funnel with pressure-equalization arm was charged with *p*-benzoquinone (3.7 mmol, 0.40 g) and 190 mL of dry diethyl ether and cooled to -78° C. The ester enolate, prepared as above, was transferred via a double-tipped needle to the jacketed funnel, maintained at -78° C and the solution added dropwise to the *p*-benzoquinone over 45 min. The mixture was allowed to gradually warm to -20° C and quenched by the addition of ethanol 95% (1.33 g, 3.7 mmol H₂O). The mixture was allowed to reach room temperature and was filtered through a florisil/anhydrous sodium sulfate pad and eluted with ether, and the solvent was evaporated *in vacuo*.

2.1.2. Spectroscopic characteristics

2, 5-Cyclohexadiene-1-acetic acid, 1-hydroxy-4-oxo-methyl ester (Jacaranone), **1**.

¹H-NMR (400 MHz, CDCl₃) δ : 1.63 (OH), 2.70 (s, 2H), 3.76 (s, 3H), 6.21 (d, *J* = 10.2 Hz, 2H), 6.96 (d, *J* = 10.2 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ : 43.2, 52.3, 67.3, 128.2, 148.7, 171.3, 184.9; IR ν_{max} (film) cm⁻¹: 3406 (OH), 2971, 2875, 1733 (C=O), 1672 (C=O), 1629 (C=C), 1049.

2, 5-Cyclohexadiene-1-acetic acid, 1-hydroxy-4-oxo-ethyl ester, **2**.

¹H-NMR (400 MHz, CDCl₃) δ : 1.26 (t, *J* = 7 Hz, 3H), 2.70 (s, 2H), 4.04 (s, 1H), 4.18 (q, *J* = 7 Hz, 2H), 6.21 (d, *J* = 10.2 Hz, 2H), 6.96 (d, *J* = 10.2 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ : 13.9, 43.7, 61.3, 67.2, 127.9, 149.3, 170.3, 185.1. IR ν_{max} (KBr) cm⁻¹: 3250 (OH), 1720 (C=O), 1670 (C=O), 1629 (C=C).

2, 5-Cyclohexadiene-1-acetic acid, 1-hydroxy-4-oxo-butyl ester, **3**.

¹H-NMR (400 MHz, CDCl₃) δ : 0.92 (t, *J* = 6 Hz, 3H), 1.51 (m, 4H), 2.68 (s, 2H), 4.10 (t, *J* = 6 Hz, 2H), 6.10 (d, *J* = 10.2 Hz, 2H), 6.97 (d, *J* = 10.2 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ : 13.3, 18.7, 30.1, 43.9, 64.8, 66.9, 127.5, 149.7, 169.7, 185.1. IR ν_{max} (film) cm⁻¹: 3675, 3450, 2950, 1720 (C=O), 1680 (C=O), 1630 (C=C).

2, 5-Cyclohexadiene-1-acetic acid, 1-hydroxy-4-oxo-geranyl ester, **4**.

¹H-NMR (400 MHz, CDCl₃) δ : 1.65 (bs, 3H), 1.70 (bs, 6H), 2.10 (m, 4H), 2.70 (s, 2H), 4.85 (d, 2H), 5.15 (m, 1H), 5.40 (m, 1H), 6.30 (m, 2H), 7.10 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ : 16.5, 17.7, 25.7, 26.2, 39.5, 43.7, 62.3, 67.4, 117.4, 123.6, 128.2, 131.9, 143.6, 149.2, 170.7, 185.1. IR ν_{max} (film) cm⁻¹, 3675, 2950, 1720, 1680, 1630; IR ν_{max}

(film) cm^{-1} : 3650, 3600, 3350, 2950, 2900, 1720 (C=O), 1670 (C=O), 1630 (C=C), 960.

2, 5-Cyclohexadiene-1-acetic acid, 1-hydroxy-4-oxo-benzyl ester, **5**

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.61 (OH), 2.74 (s, 2H), 5.18 (s, 2H), 6.18 (d, $J = 10.2$ Hz, 2H), 6.93 (d, $J = 10.2$ Hz, 2H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 43.48, 67.26, 67.45, 128.37, 128.46, 128.71, 128.72, 134.89, 148.68, 170.67, 184.81; IR ν_{max} (film) cm^{-1} : 3388 (OH), 1716 (C=O), 1671 (C=O), 1626 (C=C), 1241 (C=O); HRMS (ESI, V^+): m/z $[\text{M} + \text{H}]^+$ calc. for $\text{C}_{15}\text{H}_{15}\text{O}_4$ 259.1000, found 259.0983.

2, 5-Cyclohexadiene-1-acetic acid, 1-hydroxy-4-oxo-(2-phenylethyl) ester, **6**

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.61 (1H), 2.72 (s, 2H), 4.31 (t, $J = 6.9$ Hz, 2H), 4.42 (t, $J = 6.9$ Hz, 2H), 6.18 (d, $J = 10.2$ Hz, 2H), 6.87 (d, $J = 10.2$ Hz, 2H), 7.20-7.38 (m, 5 H); IR ν_{max} (film) cm^{-1} : 3384 (OH), 1719 (C=O), 1671 (C=O), 1626 (C=C), 1242 (C-O).

2.2. Bacteriological tests

For the diffusion methods well variant, the solvent used was dimethylsulfoxide (DMSO)

2.2.1. Test bacteria

Antibacterial activity was assessed against *Leuconostoc mesenteroides* (ATCC 8293-2), *Lactobacillus plantarum* (ATCC 14917), *Enterococcus faecalis* (ATCC 29212), *Candida albicans* (ATCC 10231), *Pseudomonas aeruginosa* (ATCC 15442), *Salmonella enteritidis* (ATCC 13076) and *Listeria monocytogenes* (ATCC 19116).

2.2.3. Suspension preparation

Each microorganism was inoculated into trypticase soy broth (TSB) + yeast (Oxoid®) and cultured at 37°C until the desired concentration was reached. The suspension of bacteria to be cultured was equivalent to 0,5 McFarland standard, ($1,5 \times 10^8$ CFU/ml).

2.2.4. Agar diffusion method

All tests were performed by duplicate. The microorganism to be tested was uniformly spreaded with sterile cotton swab over MRS agar for *L. plantarum* and *L. mesenteroides* and over trypticase soy agar plate for the other bacteria. *Candida albicans* was tested over potato dextrose agar. All agar plates were prepared using 20 ml of agar and allowed to solidify uniformly. 7 mm diameter holes were cut in the agar gel, 20 mm apart from each one. 100 μl of inoculum suspension was swabbed uniformly in the corresponding agar plates.

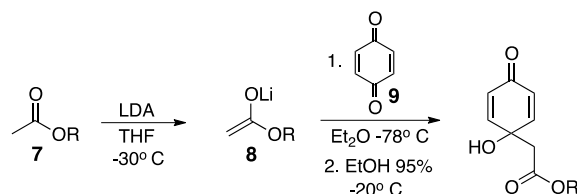
Seven serial dilutions of synthetic products, at concentrations of 10.00, 5.00, 2.50, 1.25, 0.62, 0.31 and 0.15 mg/mL were prepared. 50 μL of each dilution were added to holes. Test systems were incubated for 24 h at 35°C under aerobic conditions except for *L. plantarum* and *L. mesenteroides* that were cultured under capnophilic conditions and *C. albicans* that was incubated for 72 h. The MIC was defined as the lowest concentration of the sample that prevented visible growth. Each assay was done twice.

2.2.5. Growth curves

Growth curves for the most efficient products were determined at the Biotek Synergy HT multi detection reader (Vermont, US). Protocol followed included 600 nm lectures every 30 min for 60 h at 37° C incubation temperature. A higher concentration than CIM was used in order to establish the stability of the bacteriostatic or bactericidal effect of compounds **1** and **5**.

3. Results

The synthesis of jacaranone, **1**, and jacaranone ester side-chain analogs (**2-6**) was performed by the addition of a cold (-78° C) THF solution of the corresponding lithium ester enolates, **8**, over a cold (-78° C) ether solution of *p*-benzoquinone, **9**, as outlined in **Scheme 1**.



Scheme 1 Synthesis of jacaranone and ester analogs

The lithium enolates, **8**, were prepared by treatment of a cold (-30° C) THF solution of LDA, with the corresponding acetates, **7**. We had previously found [32] that using ethanol 95% to quench this reaction mixture, gave better results than using ammonium chloride [34]. Figure 1 shows the structure of jacaranone and side ester analogs synthesized.

Jacaranone, **1**, has been previously prepared by addition of lithium enolates, **8**, to monoprotected *p*-benzoquinone [35]. This monoprotection was done upon treatment of *p*-benzoquinone with trimethylsilyl cyanide, and after addition of the lithium enolate, the carbonyl group was unmasked by treatment with silver fluoride [36].

We prepared jacaranone, **1**, and 5 more derivatives (**2-6**, **Figure 1**) using a direct procedure (**Scheme 1**), without protection of the carbonyl group, and doing a reverse addition of enolates, **8**, to *p*-benzoquinone, **9**.

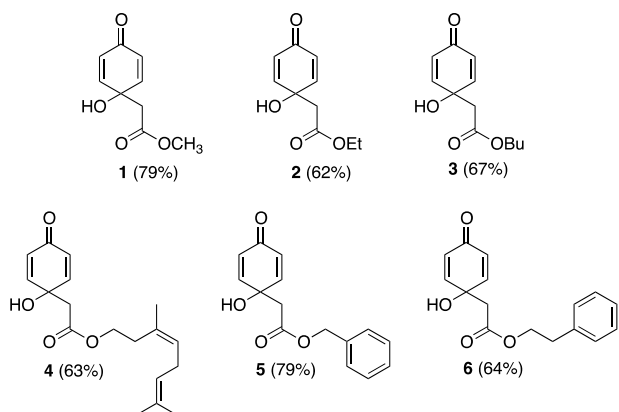


Figure 1 Jacaranone 1 and ester analogs synthesized

The antibacterial activity of these compounds was tested against Gram-positive and Gram-negative bacteria. The minimum inhibitory concentration, against different microorganisms, is shown in **Table 1**.

Table 1. Antibacterial Activity of Jacaranone, 1, and its Ester Side Chain Derivatives Against Gram-positive, Gram-negative bacteria and *Candida*.

Microorganism	Compound MIC (mg/mL)					
	1	2	3	4	5	6
<i>Staphylococcus aureus</i>	0.50	2.50	2.50	1.25	0.15	0.15
<i>Lactobacillus plantarum</i>	0.25	2.50	2.50	1.25	0.12	0.62
<i>Leuconostoc mesenteroides</i>	1.00	2.50	2.50	1.25	0.12	0.62
<i>Listeria monocytogenes</i>	0.50	2.50	2.50	1.25	0.25	1.25
<i>Escherichia coli</i>	1.25	1.25	2.50	1.25	0.25	1.25
<i>Salmonella sp</i>	1.25	2.50	2.50	1.25	0.12	1.25
<i>Pseudomonas sp</i>	0.50	-	-	10.00	0.12	5.00
<i>Candida albicans</i>	5.00	5.00	-	2.50	1.20	-

The ethyl ester derivative, 2, is also a known natural product, that has been isolated from several *Senecio* species (Asteraceae) [9, 19], and it has been reported to have activity against various tumor cell lines [19].

These results show that jacaranone, 1, and its derivatives (2-6) have activity against both, the Gram-positive and Gram-negative bacteria, with better activity against the Gram-positive organisms. Nevertheless, their activity against yeast (*Candida albicans*) was small except for product 5.

Products 5 and 6 were more active than the natural product, 1, against Gram-positive bacteria, having product 5, even a lower MIC for these bacteria.

Benzyl ester derivative, 5, shows a strong inhibitory activity against *Pseudomonas aeruginosa*, a behavior not shown by jacaranone, 1.

Candida albicans was the most resistant microorganism, only jacaranone, 1, and derivatives 2, 4 and 5 showed small inhibitory action against it, being the activity of product, 5, the most outstanding one.

Additional to the tests performed, the inhibitory activity of benzyl ester analog, 5, was tested against *Aspergillus niger* and *Fusarium sp*. The MIC obtained for *A. niger* was of 5.0 mg/mL and for *Fusarium* of 1.25 mg/mL. Also, it was tested against a multiresistant *Pseudomonas aeruginosa* clinical isolate, and it showed inhibition at a concentration of 2.5 mg/mL

Growth curve for *E. coli*, *L. monocytogenes* and *L. plantarum* in the presence of jacaranone, 1, and benzyl ester derivative, 5, are presented on **Figures 2, 3 and 4** respectively. These bacteria showed a normal growth curve (colony forming units, CFU) in the control test and a strong inhibition of its multiplication when product 5 was tested.

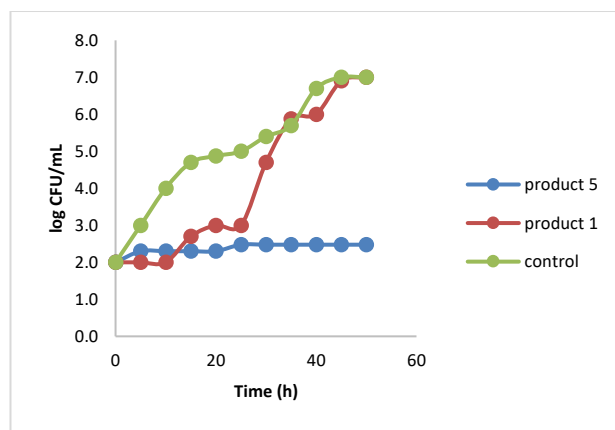


Figure 2. Growth curve for *E. coli* in the presence of jacaranone, 1, and benzyl ester derivate, 5, at a concentration of 2.5 mg/mL.

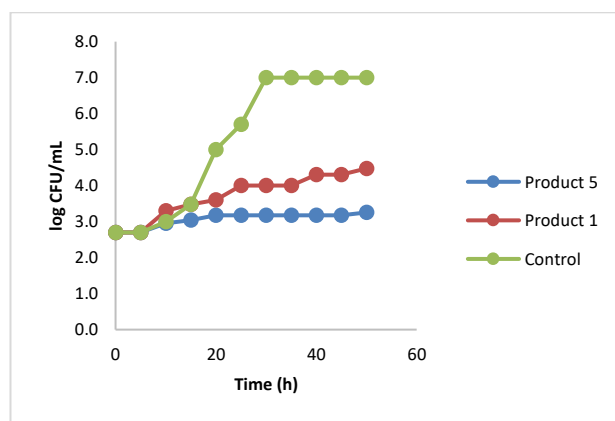


Figure 3. Growth curve for *L. monocytogenes* in the presence of jacaranone, 1, and benzyl ester derivate, 5, at a concentration of 2.5 mg/mL.

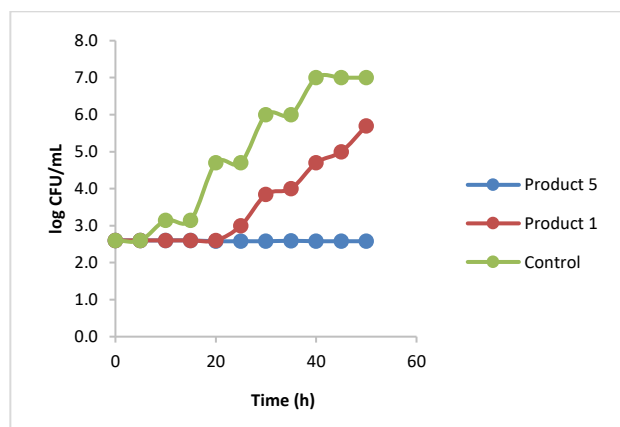


Figure 4. Growth curve for *L. plantarum* in the presence of jacaranone, **1**, and benzyl ester derivate, **5**, at 1.25 mg/mL concentration.

5. Discussion

The increase in antimicrobial resistance has been attributed to the inadequate use of antimicrobial compounds and the transference of resistance genes within and between strains [37]. This resistance has become a public health problem and includes pathogenic microorganisms but also opportunistic pathogens involved in nosocomial infections [38].

In the last years, the World Health Organization (WHO) has emphasized in the need for the development of new antibacterial compounds [39]. The development of novel, non-toxic-food compatible chemical products could help to reduce the presence of pathogens and spoilage microorganisms from environments, including surfaces, equipment and even worker hands.

Jacaranone, **1**, has been associated with antitumor activity, nevertheless little research has been done testing its antimicrobial activity [28].

The results obtained in this study showed that both jacaranone, **1**, and derivatives have an important activity against Gram-positive microorganisms, especially derivatives, **5**, and **6**, where a MIC under 0.62 mg/mL is reported for *S. aureus*, *L. plantarum* and *L. mesenteroides*. Product **5** also shows an important inhibitory activity against *Listeria monocytogenes* where a MIC of 0.25 mg/mL was obtained.

Similar preliminary results were reported by Cabezas et al [32] that found an increased activity of jacaranone, **1**, and some of its ester-side chain derivatives against Gram-positive bacteria, including *Staphylococcus aureus* and *Bacillus subtilis*.

Same way, Albayrak et al reported [40] the inhibitory activity of *Senecio* species (plants from where jacaranone has been isolated) over different microorganisms. They reported that methanolic extracts, of these plants, have a significantly higher inhibitory activity against Gram-positive than Gram-negative bacteria. Nevertheless, and contrasting with our results, they reported a null activity

against *S. aureus*. Regarding *L. monocytogenes*, they reported an important antibacterial activity for all *Senecio* taxa, achieving MICs between 6.25 and 12.5 mg of extract/mL.

Our results demonstrate that all products tested presented an important inhibitory activity also against Gram-negative microorganisms. The MIC obtained for *E. coli* was of 1.25 mg/mL for jacaranone, **1**, and derivatives **2**, **4**, and **6**, but for benzyl ester derivative, **5**, the MIC was only 0.25 mg/mL. **Figure 2** shows the growth trend of *E. coli* in the control test and in the presence of products **1** and **5** at 2.50 mg/mL concentration. Although jacaranone, **1**, has an inhibitory effect over *E. coli*, it is a bacteriostatic effect that disappears after 30 h, even when tested at a concentration twice the value of its MIC, while benzyl derivative, **5**, inhibits growth of *E. coli* even after 50 hours, showing a bactericidal effect. Same behavior is observed for *L. plantarum*, **Figure 4**, nevertheless the bacteriostatic effect of product **1** lasts only for 20 h, while derivative **5**, shows a bactericidal effect. **Figure 3** shows the effect of products **1** and **5** over *L. monocytogenes*, where a continuous bacteriostatic effect is observed for compound **1**. Product **1** allows a slight multiplication of this microorganism that might disappear when a higher concentration of the product is used. Derivative **5** showed a bactericidal effect against this microorganism, and no growth was observed even after 50 hours.

Data obtained reveals that derivate **5** inhibits bacterial multiplication through time. Contrasting, Albayrak et al [40] reported a null activity of their *Senecio* methanolic extracts against these bacteria. They also reported a negative activity against *Salmonella* spp., while our results showed that jacaranone, **1**, and derivatives **4**, **5** and **6** have an important activity against these bacteria.

Pseudomonas is a bacterium associated to different pathologies, and can easily achieve resistance to antibiotics. Benzyl ester derivate, **5**, presented a minimal inhibitory concentration of 0.12 mg/mL for this bacterium, while jacaranone, **1**, showed a MIC of 0.50 mg/mL. Albayrak et al [40] also reported this activity, but just from the methanolic extract obtained from *Senecio olympicus*. Both results can be promising for pharmaceutical industry, in order to develop products that can control these bacteria at hospital environments. The results obtained with *Candida albicans* show that derivatives **4** and **5** have an inhibitory effect over it. The MIC obtained for product **5** was of 1.20 mg/mL. Albayrak et al [40] also have reported a very poor activity of their extracts against this agent.

Additional to the tests performed, the inhibitory activity of product **5** was tested against *Aspergillus niger* and *Fusarium* sp. The MIC obtained for *A. niger* was of 5.0 mg/mL and for *Fusarium* of 1.25 mg/mL.

Also, as an additional test, a multiresistant *P. aeruginosa* clinical isolate was inhibited with a 2.5 mg/ml concentration of product **5**, an issue that deserves further

investigation because of the growing multi-resistance shown by this bacteria at hospital facilities.

Products **5** and **6** have an aromatic ring in the ester side chain, element that apparently confers the outstanding antimicrobial capacity described above.

The chemical compounds synthesized showed promising results, but it is important to take into account that MIC results may vary in the diverse studies reported in literature. This discrepancy might be due to the different methods used for the determination of antimicrobial activity combined with the use of different microorganisms and strains. Furthermore, it is well known that no strain can represent the behavior of a complete species.

The main objective of this study is to devise chemical products that can control different microorganism. The compounds analyzed in this study showed promising results, nevertheless, further studies have to be done to study the safety, solubility, as well as their stability on different food matrices.

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