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Antibacterial properties of auraptene and oxyprenylated naturally occurring benzoic and cinnamic acids

[Propiedades antibacterianas del auraptene y acidos benzoicos y cinámicos oxi-prenilados naturales]

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Abstract
The *in vitro* anti-bacterial activity of auraptene and four prenyloxycinnamic and benzoic acids was evaluated against a panel of three bacterial strain. All compounds were shown to be active as inhibitory agents of the growth of *Staphylococcus aureus*.

Keywords: anti-bacterial activity, auraptene, prenyloxycinnamic acids, prenyloxyphenylpropanoids, *Staphylococcus aureus*.

Resumen
La actividad antibacteriana *in vitro* del auraptene y de cuatro ácidos preniloxycinámicos y benzoicos ha sido evaluada sobre un grupo de tres distintas cepas bacterianas. Todos los compuestos mostraron ser activos como agentes inhibitorios del crecimiento del Staphylococcus Aureus.

Palabras Claves: actividad antibacteriana, auraptene, ácidos preniloxycinámicos, *Staphylococcus aureus*

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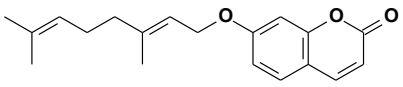
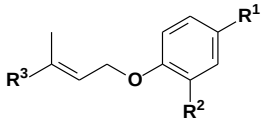
INTRODUCTION

Oxyprenylated natural products, such as isopentenyloxy- (C_5), geranyloxy- (C_{10}), and farnesyloxy- (C_{15}) related compounds, represent a family of secondary metabolites that were considered for years to be merely biosynthetic intermediates of the more widespread *C*-prenylated derivatives. These secondary metabolites have been recognized in the last two decades as interesting and valuable biologically active phytochemicals. Approximately 300 compounds have been isolated and structurally characterized from plants, primarily from the families Rutaceae, Compositae, Guttiferae, and Leguminosae, comprising several edible vegetables and fruits. The phytochemistry and pharmacology of prenyloxyphenylpropanoids was recently reviewed (Epifano *et al.*, 2007). Among these auraptene **1** (Genovese and Epifano, 2011), boropinic acid **2** (Curini *et al.*, 2008), and 4'-geranyloxyferulic acid **3** (Curini *et al.*, 2006) were shown to exert significant and appreciable biological effects as anti-cancer, anti-protozoal, anti-fungal, anti-inflammatory, and anti-oxidant agents. Aim of the current work was to study the anti-bacterial properties of these secondary metabolites together with those of two isopentenyloxycinnamic acids, namely valencic acid **4**, previously isolated from plants of the genus *Citrus*, and 4'-isopentenyloxyvanillic acid **5**, extracted from plants belonging to the genus *Tricocholea* (Epifano *et al.*, 2007).



1



2 R^1 = CH=CH-COOH, R^2 = OCH_3, R^3 = H
3 R^1 = CH=CH-COOH, R^2 = OCH_3, R^3 = isopentenyl
4 R^1 = COOH, R^2 = R^3 = H
5 R^1 = COOH, R^2 = OCH_3, R^3 = H

MATERIALS AND METHODS

Both for the chemical synthesis of compounds **1-5** (Genovese *et* al., 2009) and for the *in vitro* anti-bacterial growth assays (agar diffusion method using Muellener-Hinton agar) (Richardson *et al.*, 1968) the same general procedures as reported previously were followed. Analytical data (m.p., IR, 1H, 13C NMR, elemental analysis) for **1-5** were in full agreement with those previously reported for the same compounds (Genovese *et* al., 2009). The three bacterial strains used were *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 700926, and *Streptococcus mutans* ATCC 25175. All phytochemicals were were dissolved in DMSO and tested in the concentration range 0.5 – 62.5 μg/mL. 100 μl of 18 h bacterial cultures were used to spread a lawn on the agar. The cultures were adjusted to 10^5 CFU/ml using McFarland standard and solutions of each compound at the indicated concentration was added to each culture. The plates were left 30 min at room temperature for the diffusion of solutions containing compounds **1-5** and incubated at 37 °C for 18 h. The zones of inhibition were measured by a ruler and each experiment was repeated three times. Chloramphenicol was used as reference drug.

RESULTS AND DISCUSSION

Results of the inhibition of growth of the three bacterial strains under investigation, expresses as the minimum inhibitory concentration (MIC), are reported in the Table 1.

The five compounds under investigation exhibited a different range of activity towards the three microrganisms. *Streptococcus mutans* was the less sensible and all products can be considered virtually inactive. 4'-Geranyloxyferulic acid, valencic acid, and '-isopentenyloxyvanillic acid were only slightly active on *Escherichia coli*, while auraptene and boropinic acid were found by far less potent than these three products. The most interesting results were obtained on the growth of *Staphylococcus aureus*. All compounds exhibited a significant activity with MIC ranging from 4.1 to 6.9 μg/mL. These data are of interest considering that *S. aureus* is nowadays well recognized as one of the most dangerous bacterium able to lead to severe syndromes in humans as well as to resist to the most part of chemotherapeutics currently at disposition. In particular the phenomenon of resistance by *S. aureus* is growing all over the world (Rogers *et al.* 2011).

CONCLUSIONS

In this manuscript we studied the *in vitro* anti-bacterial properties and disclose a novel potential application of auraptene and oxyprenylated benzoic and cinnamic acids. The results obtained in the case of *S. aureus* will be further and better characterized in the next future

Table 1
Antibacterial activity of selected prenyloxyphenylpropanoids

	MIC (μg/mL)		
Compound	*Escherichia coli*	*Staphylococcus aureus*	*Streptococcus mutans*
1	30	6.9	> 62.5
2	30	4.3	38
3	10	5.3	23
4	10	4.1	41
5	10	5.3	23
Chloramphenicol	5	5	15

but, although preliminary, the data reported in this manuscript could be useful to identify novel therapeutic weapons against this extremely dangerous bacterium and prenyloxyphenylpropanoids as novel lead anti-bacterial compounds. In the mean time studies to evaluate the toxicological profile of these secondary metabolites are ongoing.

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