A187 Antimicrobial activity of the diterpene 7α-acetoxy-6β-hidroxyroyleanone and its 6β- carbamoyl derivative

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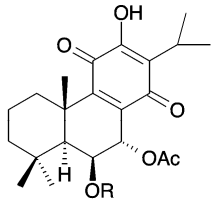

1: R = H **2 :** R = CONHCOPh

The search for antimicrobial agents namely those acting against antibiotic-resistant microorganisms is an actual concern (1). Diterpenes from *Plectranthus* sp. have revealed interesting antimicrobial activities (2). Carbamates show, in general, a wide range of bioactivity, and some hemisynthetic carbamoyl derivatives from terpenoids have been described as antimicrobial agents (3). In this work, we report a comparative study between the antimicrobial activities between 7αacetoxy-6βhidroxy-royleanone **1** and its 6β-carbamoyl derivative (7α-acetoxy-6β-(N-benzoyl)-carbamoylroyleanone) **2**. Diterpene **1**, that was isolated from *Plectranthus grandidentatus* (2) was carbamoylated to **2**, by reaction with benzoyl isocyanate (4).

The Minimum Inhibitory Concentration (MIC) was evaluated against Gram– and Gram+ bacteria and five yeast strains by the broth microdilution method, according to NCCLS (5). Compounds **1** and **2** showed moderated antibacterial activity against *Staphylococcus aureus* (MICs values 31.25 µg/ml) and weak activities against *Pseudomonas aeruginosa* and *Echerichia coli* (MICs values 125 µg/ml). Natural diterpene **1** and its derivative **2** revealed moderate antifungicidal activity against three *Candida* sp. (*C. albicans*, *C. glabrata*, *C. krusei*, MICs values 62.5 µg/ml) and weak activity against *C. tropicalis* (MIC value 125 µg/ml). Carbamoylation of diterpene **1** improved antifungicidal activity against *C. guilliermondi* (**1**, MIC value 125 µg/ml and **2**, MIC value 62.5 µg/ml).

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A188 Novel bacterial resistance modifying agents from *Lycopus europaeus* (Lamiaceae)

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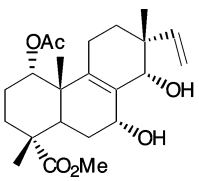
Multidrug resistance (MDR) in bacteria is an increasingly reported phenomenon and efflux mechanisms associated with methicillin-resistant *Staphylococcus aureus* (MRSA) have been described to confer resistance to macrolides (Msr(A)), fluoroquinolones (Nor(A)) and tetracyclines (Tet(K))(1). MDR MRSA is particularly difficult to treat despite the release of new classes of antibiotics such as linezolid. Whilst new antibiotics are needed to deal with the threat that MDR poses, a further approach is to find compounds that modify bacterial resistance mechanisms (2,3). These agents could be used in conjunction with existing antibiotics to which resistance has already arisen. In a project to identify and characterise natural product bacterial resistance modifying agents, we have isolated six diterpenes (typified by (1)) from the aerial parts of *Lycopus europaeus* (Lamiaceae). Two of these (methyl-1αacetoxy-7α,14αdihydroxy-8,15-isopimaradien-18-oate (**1**) and methyl-1α,14α-diacetoxy-7α–hydroxy-8,15-isopimaradien-18-oate) are novel and are reported here for the first time. Structure elucidation of all compounds was carried out using high-field NMR spectroscopy, with particular emphasis on HMBC spectroscopy. None of the isolated compounds displayed antibacterial activity at a high concentration (512 µg/mL), but in combination with standard antibiotics at 10 µg/mL, a two-fold reduction in the minimum inhibitory concentrations (MIC) of the antibiotics was observed against strains of *S. aureus* possessing the Tet(K) (tetracycline) and Msr(A) (macrolide) MDR efflux mechanisms. The activity of these compounds highlights the potential of plant derived resistance modifying agents, which may be used to restore susceptibility of strains which are multiply resistant due to MDR mechanisms.



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References: 1. Marshall, N.J. and Piddock, L.J.V. (1997) Microbiologia 13, 285-300. **2.** Gibbons, S. and Edo, E. (2000) Phytother. Res. 14, 139-140. **3.** Stermitz, F.R. et al. (2000). Proc. Natl. Acad. Sci. U S A. 97, 1433-1437.