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# *Plectranthus aliciae*: Biological activity of 6,7-dehydroroyleanone and derivatives

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

*pharmaceuticals* MDPI


**Márcia Santos Filipe[1,2], Eva Domínguez-Martín[1,2], Vera M.S. Isca[1,3], Raquel Pereira[1], Filipa Mandim[4,5], Ricardo Calhelha[4,5], Ana María Díaz-Lanza[2], Lillian Barros[4,5], Patrícia Rijo[1,3,*]**

[1]CBIOS – Universidade Lusófona's Research Center for Biosciences & Health Technologies, Campo Grande 376, 1749-024 Lisbon, Portugal.
[2]Universidad de Alcalá de Henares. Facultad de Farmacia, Departamento de Ciencias Biomédicas (Área de Farmacología; Nuevos agentes antitumorales, Acción tóxica sobre células leucémicas. Ctra. Madrid-Barcelona km. 33,600 28805 Alcalá de Henares, Madrid, España.
[3]Instituto de Investigação do Medicamento (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, 1649-003 Lisbon, Portugal.
[4]Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal.
[5]Laboratório Associado para a Sustentabilidade e Tecnologia em Regiões de Montanha (SusTEC), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal.
***** Corresponding author: patricia.rijo@ulusofona.pt


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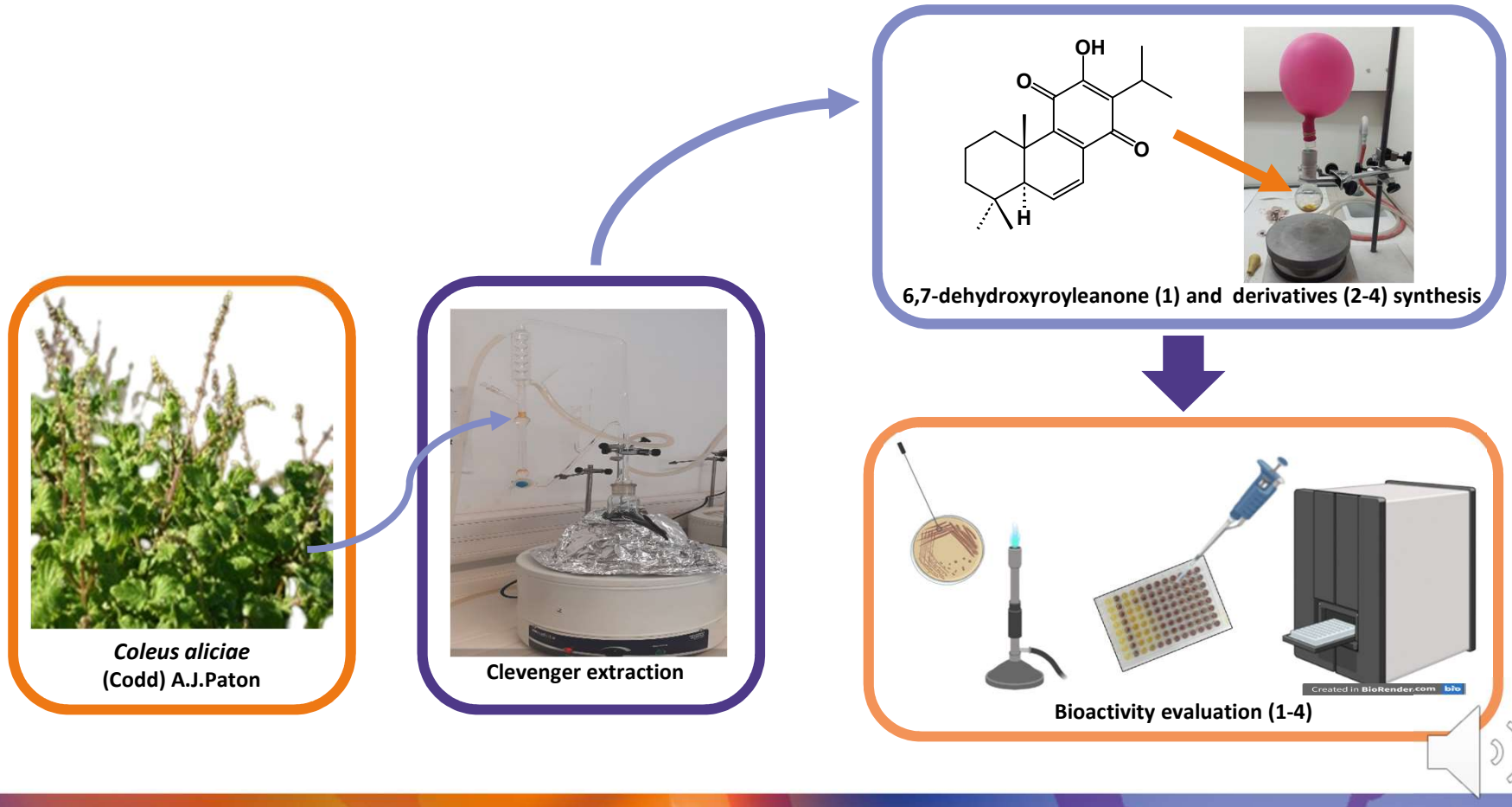
# *Plectranthus aliciae*: Biological activity of 6,7-dehydroroyleanone and derivatives



**Abstract:** *Plectranthus* genus (Lamiaceae) is known to be rich in bioactive abietane royleanone-type diterpenes, such as the 6,7-dehydroxyroyleanone (**1**), which have been previously found in *P. madagascariensis* (var. aliciae Codd). This abietane royleanone present moderate to significant cytotoxic activity against several cancer cell lines. Moreover, **1** has one hydroxyl group suitable for derivatization, that can be explored to enhance the cytotoxic potential of lead compound **1**. Based on this, the aim of the present work was to explore the obtention of **1**, from *P. aliciae aliciae (Codd)* van Jaarsv. & T.J.Edwards., a subspecie of *P. madagascariensis* to be further used in the preparation of new derivatives with enhanced biological activities. *P. aliciae* leafs hydrodestilation using a Clevenger equipment was performed, affording the essential oil (EO). **1** was assessed as the major compound of the EO, by HPLC-DAD, which was isolated and used as scaffold for esterification reactions. It was possible to obtain in three new acyl derivatives (**2** to **4**), with overall good yields (86 - 95 %). Regarding the biological activity screening, the semi-synthetic derivatives **(2-4)** improved the antioxidant activity and the cytotoxicity in MCF-7 and NCI-H460 human cancer cell lines, when comparing to **1**. Amazingly, the new esters **(2-4)** showed a promising anti-inflammatory activity, in a range of 16 to 53 times higher than **1** and also than the positive control dexamethasone. Currently, the mechanism of action and safety of the potential anti-inflammatory derivatives are under evaluation.

**Keywords:** anti-inflammatory; bioactivity; essential oil; *Plectranthus*; royleanone

# Introduction

- Belongs to the Lamiaceae family and it's a commercially important group of flowering plants.
- *Plectranthus* L'Hér. genus was more than 300 species distributed essentially in Africa, Asia, Australia, and some Pacific islands.
- *P. aliciae* has a history of traditional medicinal use by local communities to treat respiratory ailments.


**FIGURE 1.** *P. aliciae* plant: A. whole plant; B. Corolla and teethed leaves; C. Hairly ovate leaves with red glands.

Rattray, R.D.; Van Wyk, B.E. The Botanical, Chemical and Ethnobotanical Diversity of Southern African Lamiaceae. *Molecules* **2021**, *26*. | Ascensao, L., *et al.*, **1998**; Vol. 159. Rice, L.J., *et al.*, *South African Journal of Botany* **2011**, *77*, 947–959. DOI:10.1016/j.sajb.2011.07.001.

# Results and discussion

## Extraction and DHR quantification

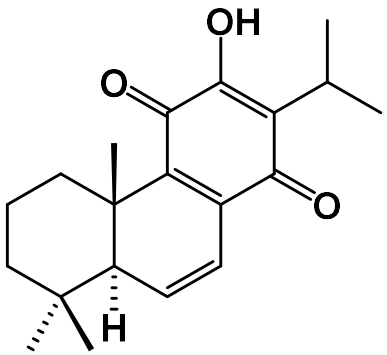



**FIGURE 2.** 6,7-dehydroxyroyleanone (DHR **1**), the major compound of *P. madagascariensis* EO and acetonic extract.

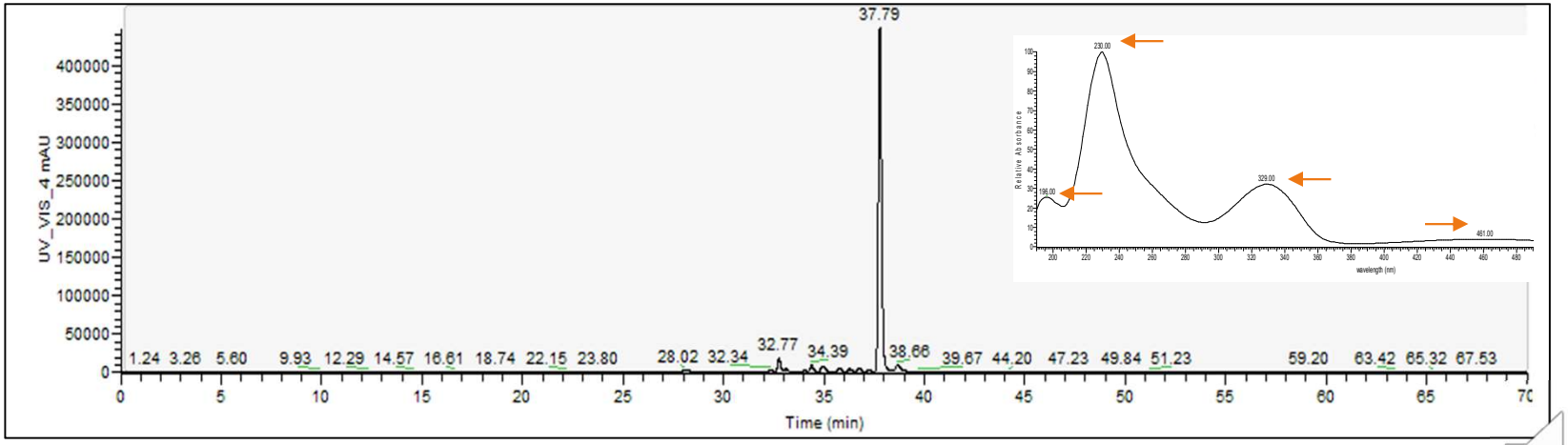



**FIGURE 3.** Extract chromatogram and UV spectra of DHR **1.**

# Results and discussion

## Bioactivity evaluation of the compounds

| Samples | ABTS $IC_{50}$ (mM) | DPPH $IC_{50}$ (mM) | ORAC (TE) | HORAC (TE) | NO $IC_{50}$ (mM) |
|---|---|---|---|---|---|
| **1** | 0.582 | > 1.5 | 0.291 | 0.294 | 0.833 |
| **2** | 0.296 | 0.685 | 0.550 | 0.608 | > 1.5 |
| **3** | 0.362 | 0.706 | 0.757 | 0.630 | 1.050 |
| **4** | 0.302 | 0.542 | 0.826 | 0.642 | 0.544 |
| **Trolox** | 0.160 | 0.221 | 1 | 1 | > 1.5 |
| **Ascorbic Acid** | 0.350 | 0.350 | - | - | - |

**TABLE 1.** Antioxidant capacity of DHR **1** and its derivatives **2** to **4**, using different methodologies.

TE- Trolox Equivalent; ORAC- Oxygen Radical Absorbance Capacity; HORAC- Hydroxyl Radical Absorbance Capacity; NO- Nitric Oxide; TAOC- Total Antioxidant Capacity.

| | *S. aureus* | | Methicillin-Resistant *S. aureus* (MRSA) | |
|---|---|---|---|---|
| **Samples** | **MIC** | **MBC** | Samples | **MIC** |
| **1** | 3.91 | 31.25 | 1 | 3.91 |
| **2** | 3.91 | >31.2 | 2 | 3.91 |
| **3** | 3.91 | >31.2 | 3 | 3.91 |
| **4** | 3.91 | >31.2 | 4 | 3.91 |
| **Vancomycin** | 1.95 | 1.95 | Vancomycin | 1.95 |

**TABLE 2.** MIC and MBC values of the compounds obtained by the microdilution method against Gram-positive strains in µg/mL.

| Samples | AGS | CaCo-2 | MCF-7 | NCI-H460 | PLP2 |
|---|---|---|---|---|---|
| **1** | 24.31 ± 1.41 | 31.62 ± 2.74 | 60.44 ± 3.69 | 82.98 ± 2.98 | 13.39 ± 0.61 |
| **2** | 20.74 ± 1.71 | 28.61 ± 0.14 | 27.45 ± 0.33 | 16.04 ± 1.68 | 27.54 ± 0.26 |
| **3** | 66.16 ± 4.49 | 20.38 ± 1.91 | 17.77 ± 0.75 | 12.99 ± 0.31 | 18.02 ± 0.19 |
| **4** | 18.53 ± 1.75 | 51.36 ± 1.56 | 38.4 5± 1.14 | 38.53 ± 3.03 | 36.07 ± 0.90 |
| **Ellipcin** | 4.99 ± 0.12 | 4.91 ± 0.08 | 4.14 ± 0.08 | 4.10 ± 0.08 | 5.68 ± 0.41 |

**TABLE 3.** Cytotoxicity results against different cell lines. $GI_{50}$ results expressed in µM.

AGS- gastric carcinoma; CaCo-2- colorectal adenocarcinoma; MCF-7- breast carcinoma; NCI-H460- lung cancer; PLP2- non-tumor cell line.

# Results and discussion

## Bioactivity evaluation of the compounds

**TABLE 4.** Anti-proliferative effect in MDA-MB-231S cancer cell line. $IC_{50}$ values presented in µM.

| Samples | $IC_{50}$ (µM) |
|---|---|
| **1** | 4.3 |
| **2** | >10 |
| **3** | >10 |
| **4** | >10 |
| **Doxorrubicin** | 0.07 ± 0.01 |

Dimethyl sulfoxide (DMSO) was used as the negative control. Doxorrubicin- positive control.

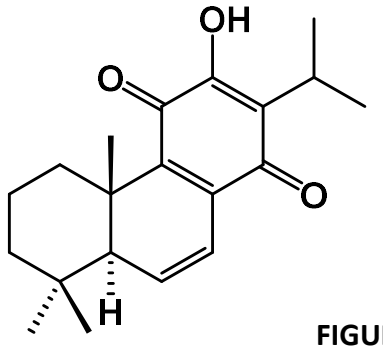
**TABLE 5.** Anti-inflammatory activity using RAW 264.7 macrophages. $IC_{50}$ results expressed in µM.

| Samples | NO Production Inhibition ($IC_{50}$ µM) |
|---|---|
| **1** | >159.00 |
| **2** | 9.94 ± 0.70 |
| **3** | 3.48 ± 0.18 |
| **4** | 4.19 ± 0.13 |
| **Dexametasone** | 16.05 ± 1.02 |

Dexametasone- positive control.

# Conclusions

- DHR **1** was the major constituent of the *P. aliciae* OE. This compound was quantified by HPLC, corresponding to 60% mg/g in the EO.
- DHR **1** was derivatized and the results showed successful esterification reactions at the C-12 moiety led to the synthesis of three compounds (**2-4**) with overall good yields (86-95%).
- The anti-inflammatory activity displayed the most promising results. Esterification at the C-12 esterification of **1** resulted in a significant increase in anti-inflammatory activity in derivatives **2** to **4.**




**1**

**FIGURE 2.** 6,7-dehydroxyroyleanone (DHR **1**), the major compound of *P. madagascariensis* EO and acetonic extr

# Acknowledgments

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