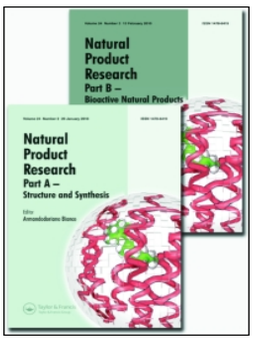

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SHORT COMMUNICATION

Isolation and X-ray structure analysis of citreohybridonol from marine-derived *Penicillium atrovenetum*

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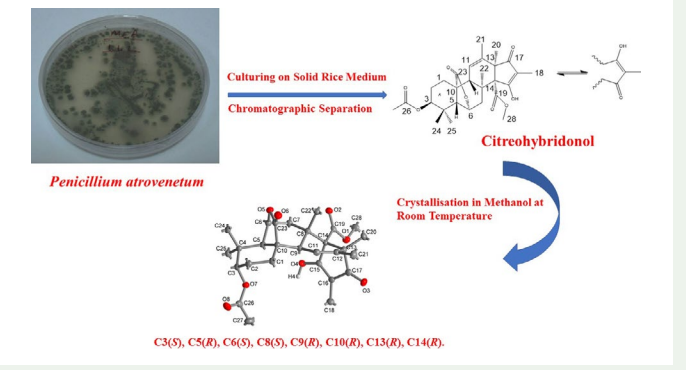
ABSTRACT

The anti-neuroinflammatory meroterpenoid citreohybridonol was isolated for the first time from a sponge-derived fungus *Penicillium atrovenetum*. In this study, in addition to isolation and structure featuring, its unambiguous absolute configuration was determined exclusively by single crystal X-ray diffraction. The C-17-keto tautomer was clearly observed in X-ray analysis. The substance crystallises in the monoclinic space group $P2_1$ with $a = 10.7496(5)$ Å, $b = 14.3286(7)$ Å, $c = 17.4909(8)$ Å, $\beta = 103.235(2)°$, $V = 2622.5(2)$ Å^3, $Z = 2$, $D_{calcd} = 1.280$ g/cm^3. The chirality of the asymmetric carbon atoms was as follows: C3 (*S*), C5 (*R*), C6 (*S*), C8 (*S*), C9 (*R*), C10 (*R*), C13 (*R*), C14 (*R*).



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KEYWORDS
Citreohybridonol; marine-derived fungi; X-ray; absolute configuration

1. Introduction

Marine-derived fungi proved to be a virtually unlimited source for many new and bioactive natural products (Hoffmeister & Keller 2007). The anti-neuroinflammatory, citreohybridonol (Cho et al. 2016) was isolated for the first time in this study from solid rice cultures of the

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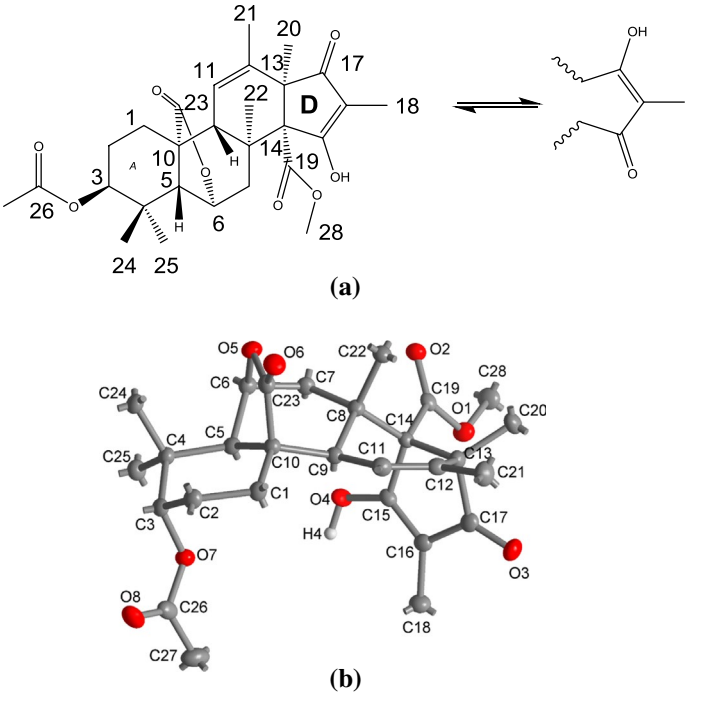

Figure 1. (a) Structures of keto-enol tautomers of citreohybridonol in polar solvents (b) Thermal ellipsoid plot (50% probability) of one of the two independent molecules (**1a**) in the crystal structure citreohybridonol. For clarity, the H atoms are only indicated as broken off bonds, except for the hydroxyl H atom. The disordered solvent molecules are not shown. The second independent molecule is given in Figure S1 in the Supporting Information. The molecule has stereocenters at the following carbon atoms (absolute configuration given in parentheses): C3 (*S*), C5 (*R*), C6 (*S*), C8 (*S*), C9 (*R*), C10 (*R*), C13 (*R*), C14 (*R*).

sponge-derived fungus *Penicillium atrovenetum*. Interestingly, this compound was reported to exist in an equilibrium between two tautomers of ring D (Figure 1(a)) in NMR solvents such as $CDCl_3$ and CD_3OD, resulting in difficulties in assignments of NMR signals (Kosemura 2003). The reasons for tautomerism in natural products were reported to be due to experimental conditions (temperature, light etc.) and/or molecular interactions between polar solvents and compounds, for example in prototropy, the relocation of a proton, often catalysed by acids or bases (Pettit et al. 2003). However, when optimising the experimental conditions, there is the possibility that only one main tautomer dominates and in this case the structure and configuration of this tautomer can be determined via X-ray crystallography (Slabber et al. 2016). In this study, the structure of citreohybridonol was elucidated and the C-17-ketone-tautomer in DMSO-d_6 was found to be the major tautomer. Nevertheless, tautomerism was observed at ring D which corroborates reports from the literature (Figure 1(a)). Herein, we report for the first time, the optimum conditions for crystallisation, structure elucidation and for the unambiguous assignment of the absolute configuration of the dominant tautomer of citreohybridonol in solid crystal by X-ray crystallograpic analysis. As a result, there is only structure **1a** (Figure 1(b)) that is detectable in its crystal. These results present a configurational standard for the structural elucidation of related members of this class of compounds.

2. Results and discussion

Citreohybridonol (**1**) was obtained as colourless crystals. The UV spectrum showed λ_{max} (MeOH) at 212.9 and 258.3 nm; α_D^{20} + 32 (*c* = 0.07, $CHCl_3$); HRESIMS $[M + H]^+$ *m/z* 501.2480 (calcd for $C_{28}H_{37}O_8$, 501.2483). The NMR data (DMSO-d_6) (see Table S4 in Supporting Information).

Compound **1** crystallised from methanol with two symmetry-independent molecules in the asymmetric unit together with disordered methanol/water solvent molecules. Figure 1(b) depicts one of the two independent molecules; the second one is shown in Figure S1 in the Supp. Info. Both independent molecules have the same absolute configuration (see caption to Figure 1 and Figure S1). The obvious and major conformational difference between the two molecules is the torsion angle of the methyl ester group on C3 and C31. In molecule **1** this torsion angle, defined as C4–C3–O7–C26 is −157.6(2)°, while in molecule **2** the corresponding torsion angle at C32–C31–O15–C54 is −105.5(2)°. Another difference is the hydrogen bonding interaction of the hydroxyl group. The O4–H4 group in molecule **1** is a donor to O16=C of the aforementioned methyl ester group. While the O12–H12 group in molecule **2** is a donor to a solvent oxygen atom (O17, not shown in the figures). Details of the hydrogen bonding are given in Table S2 in the Supporting Information.

Two symmetry independent molecules in the asymmetric unit, monoclinic, space group $P2_1$, *a* = 10.7496(5) Å, *b* = 14.3286(7) Å, *c* = 17.4909(8) Å, *β* = 103.235(2)°, *V* = 2622.5(2) Å^3, *Z* = 2, D_{calcd} = 1.280 g/cm^3, crystal size 0.06 × 0.06 × 0.06 mm^3, Cu-Kα (*λ* = 1.54178 Å). *F*(000) = 1108, *T* = 140(2) K. The final *R* values were R_1 = 0.0294 and wR_2 = 0.0753 for 8658 reflections with $I > 2\sigma(I)$ and R_1 = 0.0296 and wR_2 = 0.0756 for all 8766 independent reflections with 697 parameters. The absolute structure (Flack) parameter was 0.06(3) indicating the correct refinement of the absolute structure. The structure contains disordered solvent molecules, which could not clearly be refined and assigned (Flack 1983, 2003; Flack & Bernardinelli 1999, 2008; Flack et al. 2011) The structural data have been submitted to the Cambridge Crystallographic Data Center and the code (CCDC-No 1513699) was obtained.

3. Conclusions

The designation of the present research succeeded to present the unambiguous absolute configuration of citreohybridonol as a standard for the structural elucidation of related compounds.

Supplementary data

Experimental part including full details of the crystal structure of citreohybridonol in addition to its spectroscopic data are included in the supplementary data.

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Disclosure statement

No potential conflict of interest was reported by authors.

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