

## Antiplasmodial bisabololoxide derivatives from *Artemisia persica*; determination of the absolute configurations by ECD

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**Background and Aims:** Malaria, a protozoan disease caused by Plasmodium parasites, is a major health problem for large areas of the world. In Iran, Artemisia species have been traditionally used for treatment of intermittent fever and chills which are the main symptoms of malaria. We here report on the isolation of antiplasmodial constituents of Artemisia persica, and the structure elucidation including determination of the absolute configurations of active compounds.

**Methods:** Antiplasmodial activity of an EtOAc extract of *A. persica* was localized by HPLC-time-based activity profiling. Briefly, 350 µg of the extract was separated by analytical gradient HPLC. The one-minute microfractions were submitted to the bioassay. Subsequently, the peaks in the bioactive time-window were isolated using different chromatographic methods. Structure elucidation was achieved by HR-ESIMS, 1D and 2D NMR experiments. The relative configurations were established on the basis of 3JH-H coupling constants and NOE difference spectra while the absolute configurations were assigned by comparison of experimental electronic circular dichroism (ECD) spectra with simulated data for possible stereoisomers.

**Results:** Five new bisabololoxide sesquiterpene diesters were isolated from EtOAc extract of the aerial parts of *A. persica*. Structures of the bioactive compounds were characterized by extensive NMR experiments. Relative and absolute configurations of cyclohexenone/cyclohexene and tetrahydropyran moieties of 1-5 were established. Four sesquiterpenes exhibited antiplasmodial activity with IC<sub>50</sub>s ranging from 1.2 to 8.8 µg/ml, and selectivity indices (SI) in L-6 cells of 3.68 to 11.9.

**Conclusions:** Antiplasmodial constituents of *A. persica* were identified as highly oxidized sesquiterpene derivatives. Bisabololoxides are a rather rare type of sesquiterpenoids limited to some sections of the family Asteraceae. Herein, the first ECD analysis of bisabololoids was performed. The quality of predicted ECD data critically depended on a careful conformational analysis.

**Keywords:** *Artemisia persica*; *Plasmodium falciparum*; Bisabololoxide; ECD