

**A new COX-2 inhibitory agent isolated from
Achillea millefolium L. s.l. and *Matricaria recutita* L.**

Susanne Goeters[#], Klaus Lohmann⁺, Peter Imming[#], Bernd Hempel^{*}

**[#]Institut für Pharmazeutische Chemie, Philipps-Universität Marburg,
⁺Institut für Pharmazeutische Biologie, Heinrich-Heine-Universität Düsseldorf
^{*}Robugen GmbH, Esslingen**

Objective:

Extracts of *Millefolii herba* and *Matricariae flos* possess anti-inflammatory properties. Chamazulene carboxylic acid (**1**) is a degradation product of sesquiterpene lactones from Asteraceae. We previously showed **1** to have a striking constitutional similarity with profens. We here present investigations concerning its stability, effectiveness and mechanism of action.

Materials and methods:

- flowers of *Millefolii herba* (*Achillea collina* BECKER PROA.) and *Matricariae flos* ('Mabamille')
- ¹H NMR, first-order kinetics
- sheep COX-1 and COX-2
- rat paw edema

Results:

1 decarboxylated considerably faster at acid pH than in neutral solution, but was quite stable at blood pH. In order to stabilize **1** for oral application, ester prodrugs were synthesized.

At 50 µM, **1** did not inhibit COX-1, but COX-2 (43.5%), thus being equipotent to the reference substance, nimesulide (Aulin®, Boehringer Mannheim Switzerland). After oral application, **1** had a slight inhibitory effect one hour after carrageenan treatment (17.4% at 300 mg/kg), while its ester prodrugs were more potent (22.8% and 34.8% at 300 mg/kg). Acetylsalicylic acid caused a pronounced effect (92.4% at 600 mg/kg).

Conclusion:

We have shown the proazulenes to be important, not only as a marker for constant quality of drug batches, but for the anti-inflammatory action of the drug and drug extracts. Future ESCOP and Ph. Eur. monographs should take account of this. For the therapeutic usage this implies that cultivars and extracts with a high proazulene content should be used.