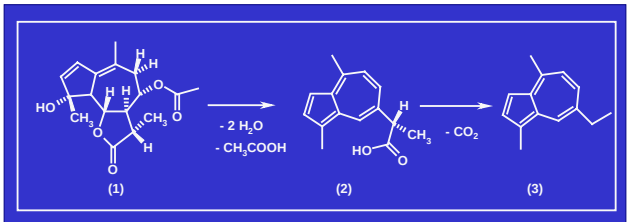
Anti-Inflammatory Proazulenes and Azulenes from Chamomile

M. Ramadan[a]*, P. Imming[a], B. Hempel[b], Y.-Y. Ford[c]
[a] Institut für Pharmazeutische Chemie, Philipps–Universität Marburg, Germany
[b] Robugen GmbH Pharmazeutische Fabrik, Esslingen, Germany
[c] Horticulture Research International, West Malling, Kent, UK

Introduction:

Chamomilla recutita L. Rauschert, the sun loving plant of the plains, is rich in active ingredients and has remained one of the most popular herbs since ancient times. Due to the characteristic aroma of its fresh flower the Greeks called it `kamai melon`, the ground apple. Hippocrates described this herb as helpful in the treatment of congestion and dysmenorrhea. Dioskurides, Galen and Plinius also recommended chamomile tea for stomatitis, and a bath with chamomile infusion or tincture in cases of painful menstruation. Today, the primary uses of chamomile are due to its antispasmodic, antiphlogistic and sedative effects. Among the active antiinflammatory components are matricin and its degradation products, the azulenes.[1]

1. Matricin:



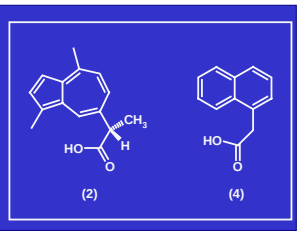
Matricin (1), a sesquiterpene lactone compound, is present essentially in the linguiform ray florets and tubular disc florets of chamomile flower. Upon steam destillation it is readly converted into chamazulene carboxylic acid (2) and further into chamazulene (3). Matricin and chamazulene were examined and their antiphlogistic action has been proved in a variety of experimental inflammatory reactions.[2] Chamazulene carboxylic acid has received no attention since it was identified in 1953.[3]

2 . Chamazulene carboxylic acid:

Chamazulene carboxylic acid (2) is a naturally occuring profen with *S*-configuration and selective COX-2 inhibitory properties. The pharmacokinetic parameters of (2) show that (2) should be absorbed after oral administration, but it is chemically unstable esp. in acidic media. Ester derivatives of (2) were synthesized. They exhibited a weak antiinflammatory effect and a short duration of action.[4]

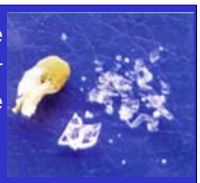
3. Anti-auxin effect:

A bioassay, which depends on ethylene production from pea internodes to indicate the auxin activity, was used to examine the effect of chamazulene carboxylic acid (2). 1-naphthylacetic acid (4) was used as a standard auxin. (2) and (4) are structurally related. (2) was shown to have a weak auxin effect. When (2) was mixed with (4), it acted as a competitive inhibitor and exhibited anti-auxin effects.



4. Matricin extraction:

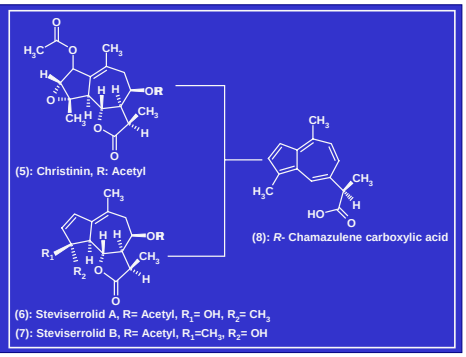
The following chamomile cultivars were assayed for matricin content by quantitative TLC scanning.



Cultivar	Year	Matricin mg/g dried flower heads
Mabamille	2001	1.2
Mabamille	2002	0.6
Mabamille	2003	0.8
Kirsch	2003	1.2
Manzana	2003	1.8

5. Stereochemical considerations:

The configuration of a drug is an important determinant of its effects. Chamazulene carboxylic acid from chamomile has the *S*-configuration like profen eutomers. The *R*-enantiomer (8) was extracted from Stevia serrata Cav., which contains the proazulenes (5), (6) and (7). Using lanthanide shift reagent, we proved the purity and stereochemistry of (8).



6. In-vitro testing:

In artificial gastric fluid, after 30 min. no matricin was detectable. 50% of it was transformed to chamazulene carboxylic acid, but no chamazulene. In contrast, matricin was not degraded in artificial intestinal fluid after 60 min. These results show that matricin should be a good precursor for chamazulene carboxylic acid by oral application.

7. Results and further studies:

The antiphlogistic effect of matricin has been known for a long time. Due to its lability in body fluids, it cannot be responsible for this action. Which of the degradation products of matricin, the azulenes, is indeed the active principle in this process? To answer this question, more studies are needed.

References:
[1] Schilcher, H. *Die Kamille.* Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1987.
[2] Hitziger, T.; Höll, P; Ramadan, M.; Imming, P. *Pharm.Ztg.* **2003**, 148, 372-380.
[3] Stahl, E. *Chem. Ber.* **1953**, 87, 202-205.
[4] Chamazulencarbonsäureverbindungen und deren Verwendung. Ger. Offen. DE 10065683 A 15 Jul 2001 (*Chem.Abstr.* **2001**, 135, 76647)