

COMMUNICATION

THE STRUCTURE OF FLAVONE-8-ACETIC ACID, A CHEMOTHERAPEUTIC AGENT, AND ITS APPLICATION TO DRUG DESIGN

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Flavone-8-acetic acid (NSC-347512) is a new agent with high activity against colon adenocarcinoma 38 in mice¹ and is recommended as a prototype for other solid tumors.^{2,3} Flavones in general⁴ and positional isomers such as the 3, 5 and 7-acetic acids (data from the files of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute) have not shown such *in vivo* activity. The unique character of the 8-acetic acid isomer is indicated by its resonance form shown in Figure 1. The structural constraints of the molecule stabilize the oxonium and carboxyl groups as the intimate ion pair of the heterolytic cleavage of an acyl peroxide and introduce a reductive site at the oxygen on position 4. This is confirmed by the observation that flavone-8-acetic acid instantaneously reduces 2,6-dichlorophenol-indophenol in alkaline medium, while flavone itself or the 3, 5 and 7-acetic acid isomers do not. Reduction by all flavones occurs on standing overnight, but only the 8-acetic acid yields a deep yellow chromophore.

The suggestion is made, as shown by the dotted line in Figure 1, that pyrone-2-

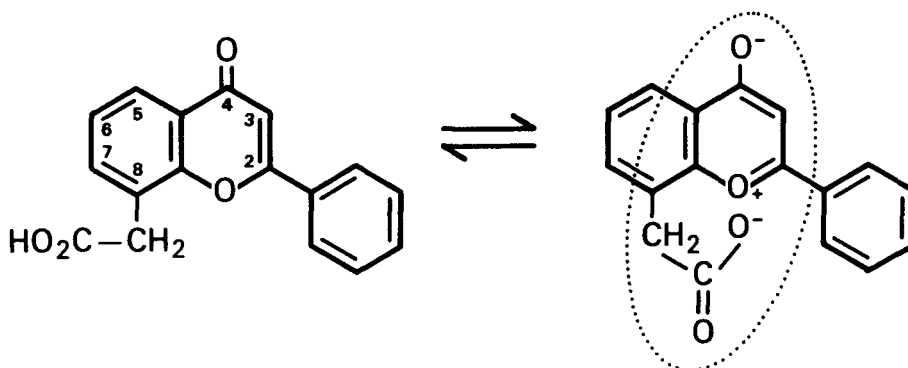


FIGURE 1 Flavone-8-acetic acid. The putative active moiety is indicated by the dotted line.

propionic acid may be the active moiety for chemotherapeutic activity, and indicates its synthesis and testing for biological activity as well as that of the cis-acrylic acid and L-alanine congeners and more complex structures containing such functions.

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References

1. J. Plowman, V.L. Narayanan, D. Dykes, E. Szarvasi, P. Briet, O.C. Yoder and K.D. Paull. *Cancer Treatment Rep.*, **70**, (5), 631 (1986).
2. D.S. Zaharko, C.K. Grieshaber, J. Plowman and J.C. Craddock. *Cancer Treatment Rep.*, **70**, (12) 1415 (1986).
3. T.H. Corbett, M.-C. Bissery, A. Wozniak, J. Plowman, L. Polin, E. Tapazoglou, J. Dieckman and F. Valeriote. *Invest. New Drugs*, **4**, 207 (1986).
4. B. Havsteen. *Biochem. Pharmacol.*, **32**, (7) 1141 (1983).