

Figure 1 Some naturally occurring and synthetic cytotoxic agents that bind to microtubules.

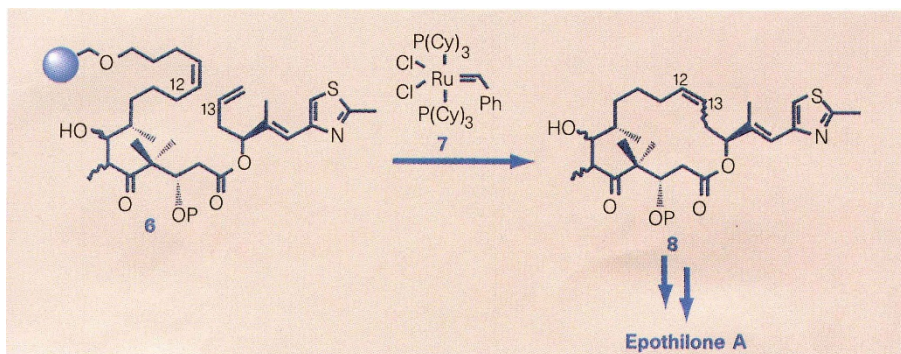


Figure 2 Olefin metathesis: a key step in the solid-phase synthesis of epothilone A, which in the process cleaves the linking chain to the resin bead (P = *t*-BuMe<sub>2</sub>Si; Cy = cyclohexyl).

um catalyst 7 (ref. 8), which simultaneously generates the 16-membered macrocycle 8 and cleaves the polymer support. Although this process has been widely used in polymer synthesis, its potential in the construction of complex ring systems is only now being realized. Its application to the epothilone system has also been demonstrated independently by Danishefsky and Schinzer<sup>4</sup>.

The accompanying synthesis<sup>5</sup> of epothilone B (3 in Fig. 1) is more traditional, in that a C15–O bond formation (a macrolactonization) is employed to form the large ring. In contrast, in the first reported synthesis<sup>9</sup> of epothilone B, Danishefsky and co-workers used an unusual intramolecular aldol reaction at C2–C3 to close the macrocycle. Both these syntheses proceed via alkene 4 with a selective epoxidation as the final step.

Now that the synthesis of both epothilones has been achieved, chemists and biologists can begin to find out what features of the compounds are essential for their activity. Already, compound 4 has been found to be more active than either taxol or the epothilones in a tubulin-assembly assay, indicating that the epoxide may not be essential for microtubule stabilization<sup>5,9</sup>. A library of further epothilone analogues can now be produced by varying the existing

synthetic routes<sup>4,5,9</sup>, and those analogues with strong antiproliferative properties can go on to clinical evaluation. Unlike the early stages in the development of taxol<sup>3</sup>, which was originally extracted from the bark of the Pacific yew, work should not be hindered by the availability of these compounds. It is to be hoped that a promising epothilone analogue will retain its activity *in vivo*.

The unfinished epothilone story is yet another illustration of the wealth of biological activity associated with natural products, and the ingenuity of synthetic chemists in constructing complex molecules. As for whether the epothilones turn out to be better than taxol at fighting cancer, it is far too early to say. □

Cameron J. Cowden and Ian Paterson are at the University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK.

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100 YEARS AGO

Messrs. John Walker and Co., Ltd., have sent us several packets of their "Perfection Envelope," which have been designed to do away with the necessity of licking, or otherwise moistening, the gum on the flap of an envelope in order to make it adhere. The gum is placed upon the back of the envelope instead of on the flap, so that by moistening the flap the envelope can be sealed without touching the gum with the tongue. The advantage thus gained is not very clear, for it is possible in the case of any envelope to moisten the back instead of the gummed flap. What is really required is a simple device for sealing envelopes without going through the very objectionable practice of licking them.

From *Nature* 13 May 1897.

50 YEARS AGO

It has been known for a long time, particularly from the work of Schuster, Sutherland and H. A. Wilson, though lately little regarded, that the magnetic moment *P* and the angular momentum *U* of the earth and sun are nearly proportional.... We can write, in fact,

$$P = \beta \frac{G^{1/2}}{c} U,$$

where  $\beta$  is a constant of the order of unity.

For the first time, the magnetic field of a star, 78 Virginis, has recently been measured (Babcock, 1947). Using the best estimate available for its mass, radius and rotational velocity, the calculated value of the magnetic field agrees with its observed value. We have, therefore, a rough verification of the equation above for three bodies, the earth, sun and 78 Virginis, and covering a range of *P* and *U* of more than 10<sup>10</sup>:1, though only of 2,000:1 in measured field. It is therefore considered that the above equation must be taken seriously as a possible general law of Nature for all massive rotating bodies. ...

It is suggested tentatively that the balance of evidence is that the above equation represents some new and fundamental property of rotating matter. Perhaps this relation will provide the long-sought connexion between electromagnetic and gravitational phenomena.

Prof. P. M. S. Blackett, F. R. S.  
From *Nature* 17 May 1947.