TAXOL

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"Catocoluus, jefe de los Eburones, se ha suicidado tomando extracto del tejo"

(*Taxus baccata*)

Libro IV. Guerra de las Galias
Julio César

HITOS

1960. – El INC inicia un programa sobre la búsqueda de tumorales de origen vegetal (L. Hartwell)

1962. – El departamento de Agricultura USA recolecta 650 muestras (A.S. Barclay) en California, Washington y Oregon. Entre las muestras una de corteza de Taxus brevifolia (Estado de Washington).

1963. – Se remiten a M.E. Wall unas muestras de extractos de Tb para su estudio de farmacognosia al haber detectado citotoxicidad en células 9KB (tumor humano nasofáríngeo) (Wall había detectado correlación en la citotoxicidad entre 9KB y L1210)

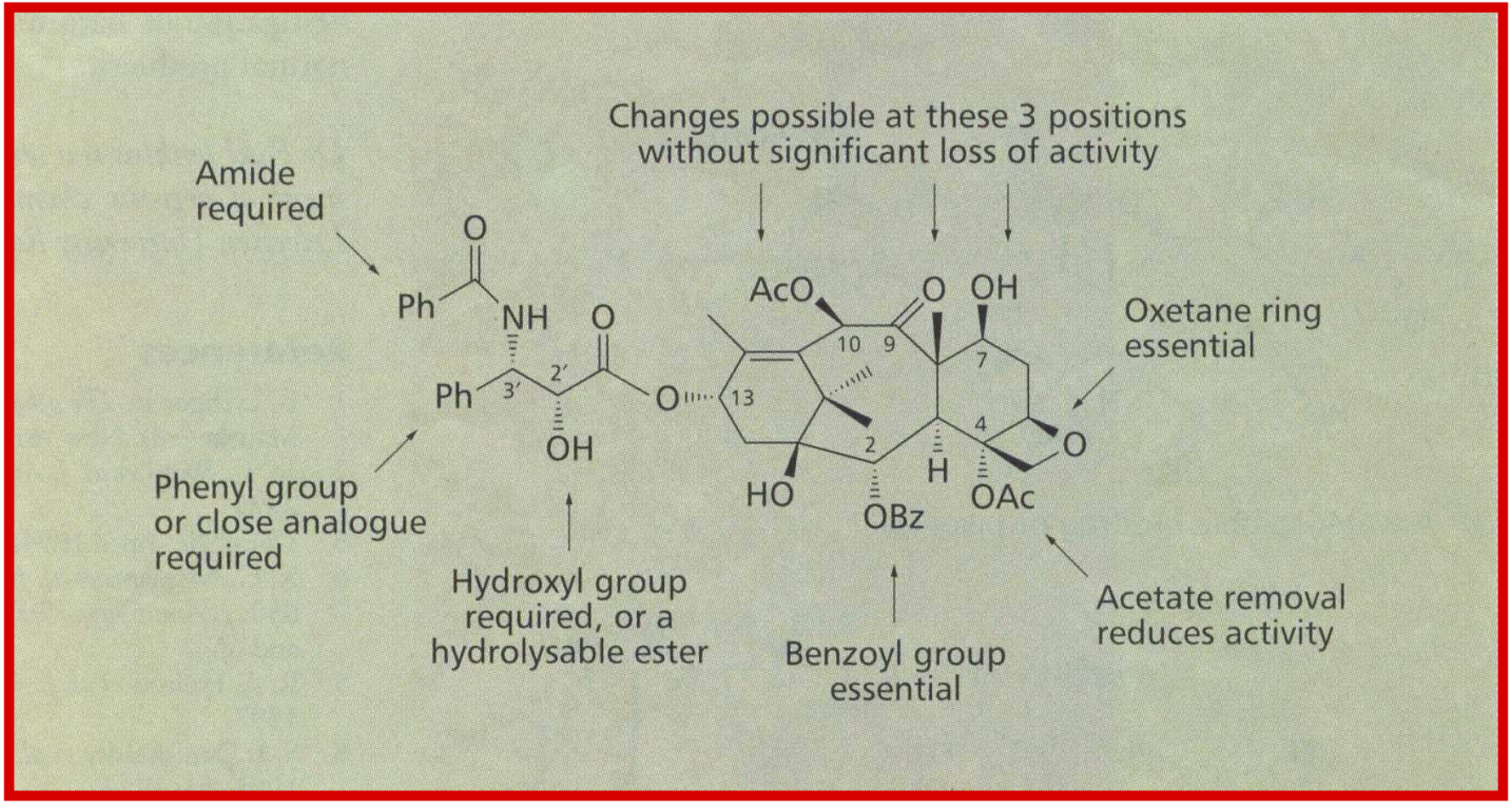
1964. – En el laboratorio de Wall sobre 12 kilos de corteza de *Taxus brevifolia* secado al aire.

Extractos de etanol (95%) → concentrado →

Partición H_2O y Cloroformo – metanol (4:1) →

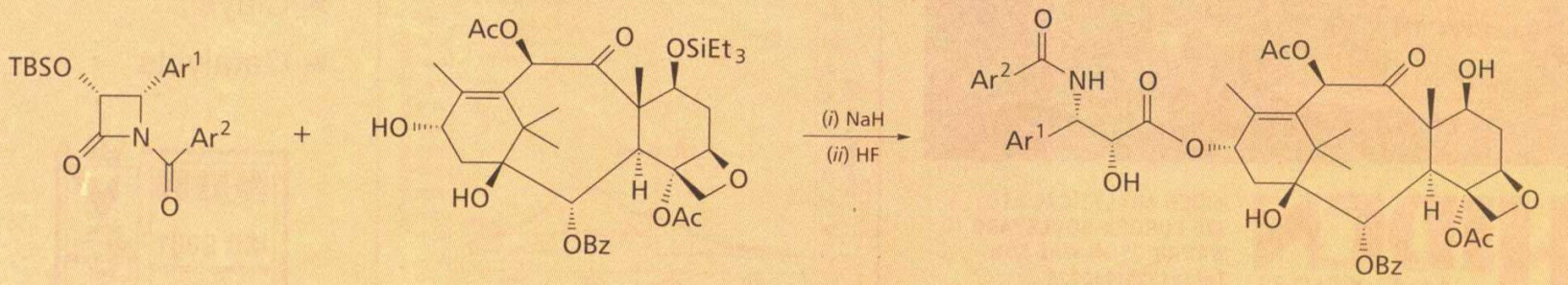
Cloroformo (146 g sólidos; actividad en tumores sólidos 5 Walker WM, T/C= 31% a 100 mg/kg)

Rendimiento en taxol: 0,004 %



Chem. Britain

Scheme 1 The semi-synthesis of taxol analogues from modified side chains and protected baccatin III



β-lactam side chain precursor (*5*)

7-triethylsilylbaccatin III (*6*)

General structure of a series of taxol analogues (*7*)

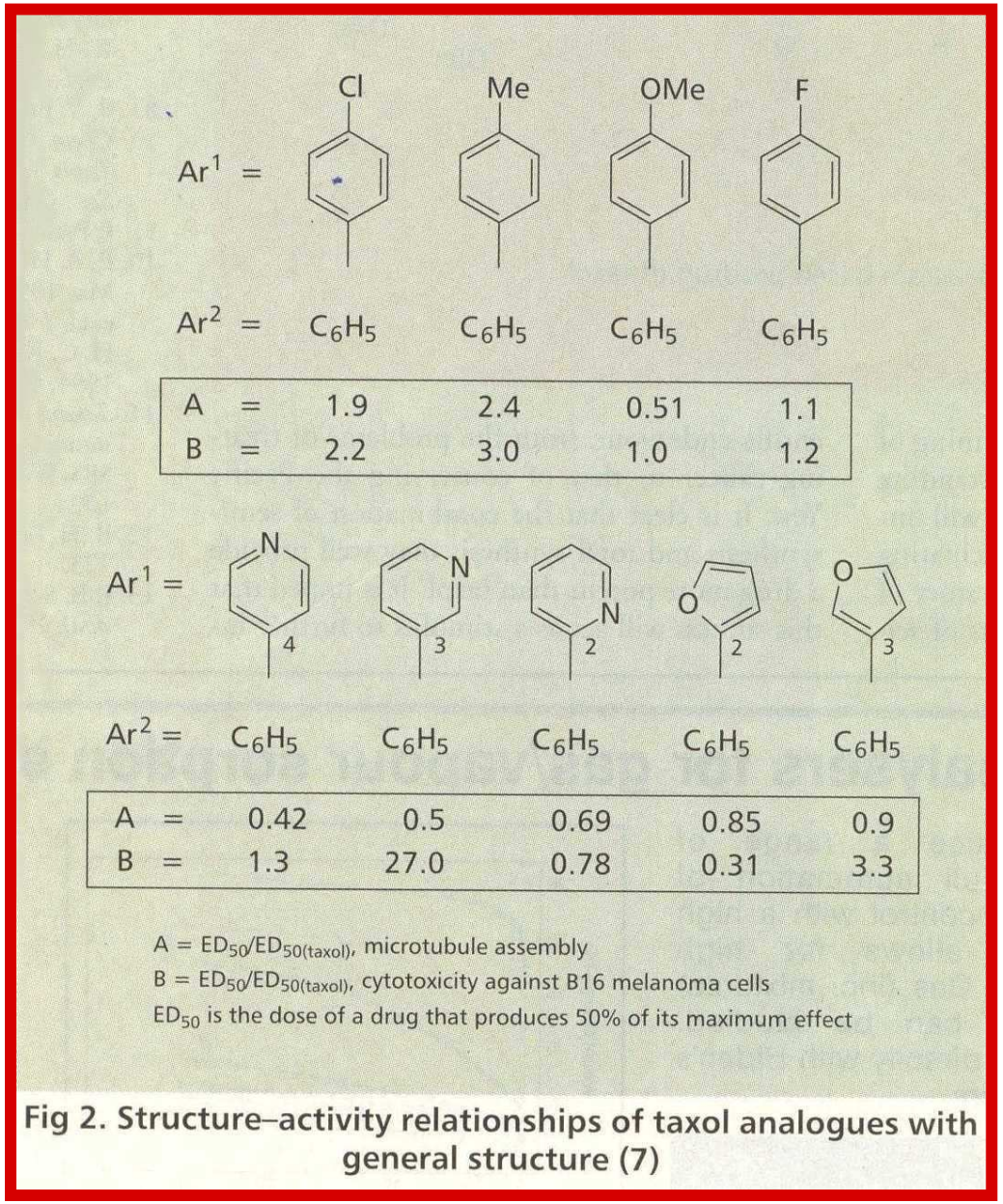
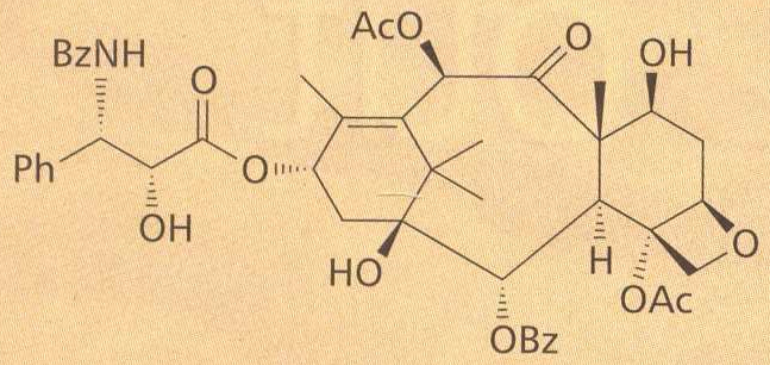
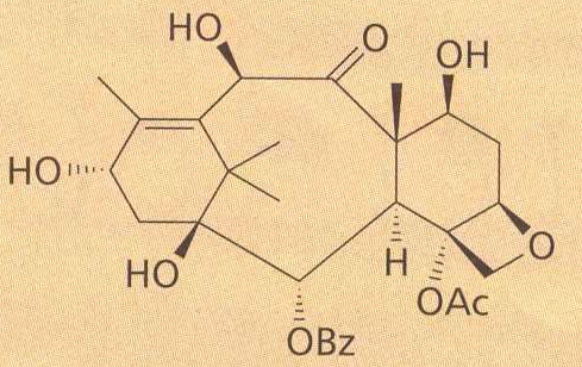


Fig 2. Structure–activity relationships of taxol analogues with general structure (7)

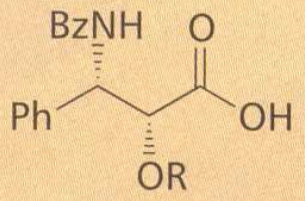
Taxol and related compounds



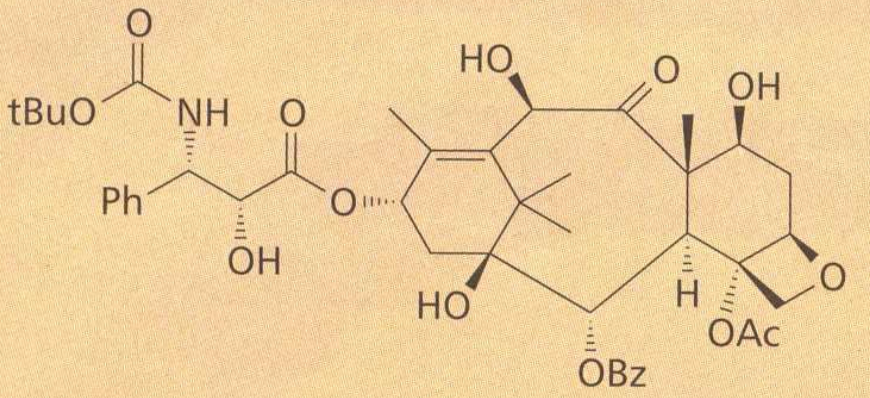
Taxol (*1*)



10-Deacetyl baccatin III (*2*)

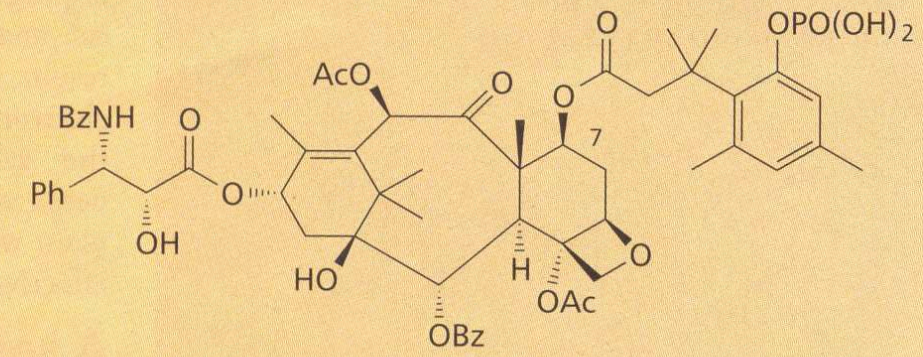


Side chain (*3*)

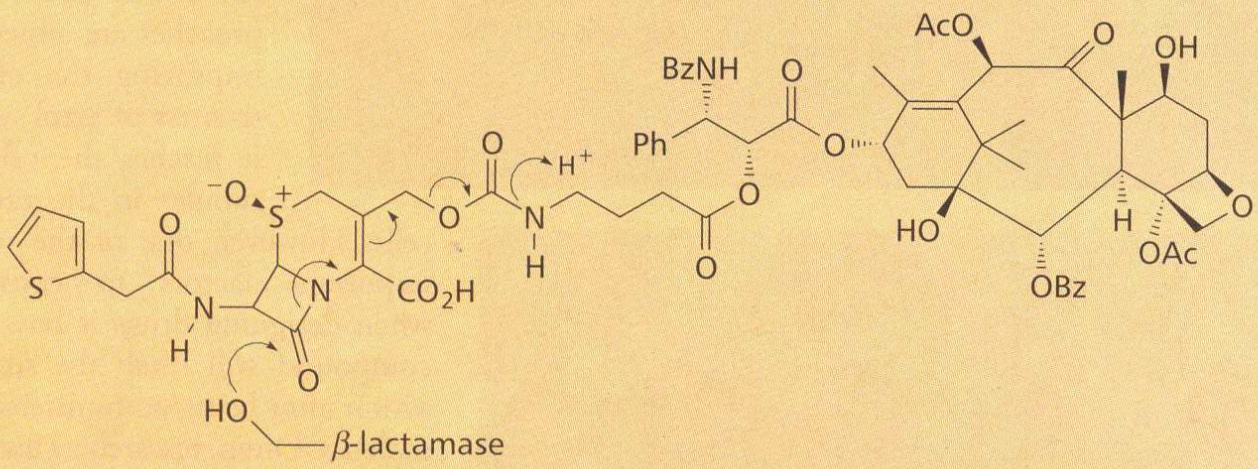


Taxotere (*4*)

Prodrugs of taxol



A water-soluble prodrug of taxol (*8*)



Protax (*9*), a β-lactam based prodrug of taxol

Table 1. The development of taxol as an anti-cancer drug

1962–66	US National Cancer Institute (NCI) programme of natural product screening for cytotoxicity and anti-leukaemia activity
1969	Pure taxol isolated
1971	Wani and Wall report the anti-leukaemic properties of taxol
1979	Susan Horwitz reports that taxol stimulates microtubule assembly
1983–90	Phase I and II clinical trials for all types of cancer – most favourable results obtained for breast and ovarian cancer
1991	US NCI initiative to develop taxol as an anti-cancer drug
1991–95	Further extensive hospital trials and application for US Federal Drug Administration approval
1994	The first total syntheses of taxol by Nicolaou and Holton

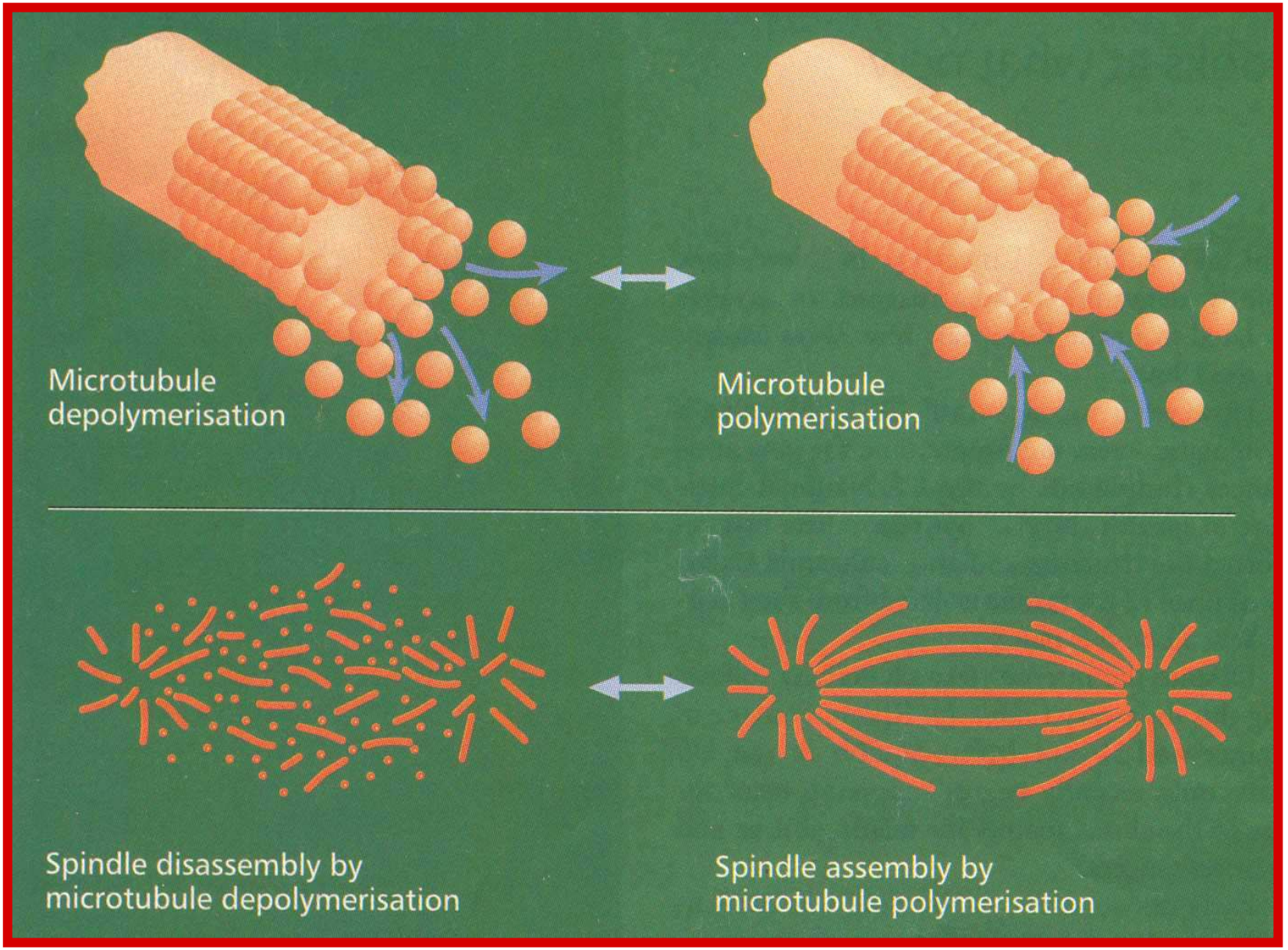
What does taxol do?

All plant and animal cells that have a nucleus (eukaryotic cells) contain a protein called tubulin. Tubulin has many functions in the cell which arise from its property of polymerising to form microtubules. For most of the cell's life, these microtubules are a kind of cell skeleton and make up the organs of movement. However, when cell division is about to take place microtubules depolymerise back to tubulin and re-polymerise to form the spindle of cell division (*see Fig*). The function of this spindle is to push apart the two new cells that are formed from the original cell and to act as a framework on which the chromosomes of the original cell are distributed from the nucleus of the original cell to the nuclei of the daughter cells.

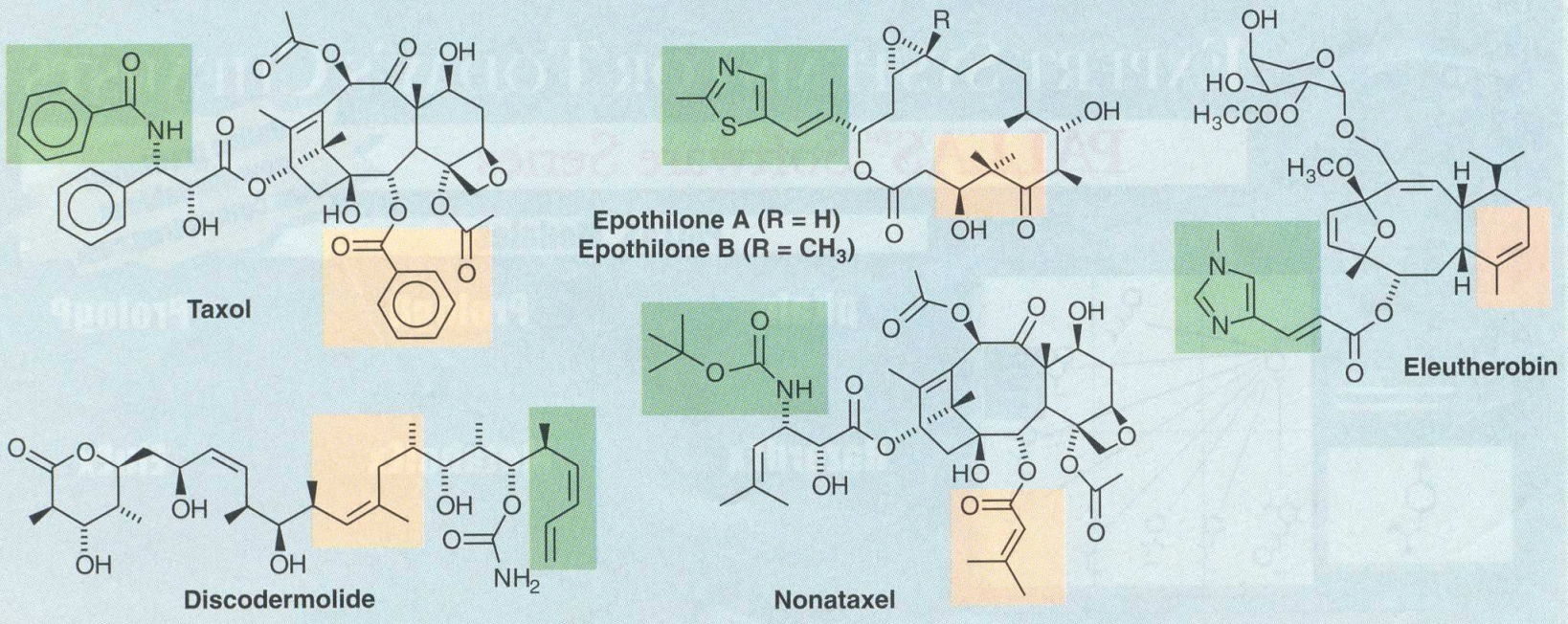
Most ordinary body cells divide only very infrequently; cancer cells on the other hand divide very rapidly, producing layers of cells that ultimately form lumps and tumours. One of the major differences between normal cells and dividing cells is the function of the tubulin. Many cancer chemotherapy agents, for example vincristine, vinblastine, podophylotoxin and maytansine, act as spindle poisons and prevent the formation of a normal spindle in cell division.

Taxol, however, has a rather different mode of action. In 1979 Susan Horwitz from Albert Einstein College, New York, showed that taxol stimulates the formation of microtubules and prevents their breakdown.[13] Although at first it might seem strange that substances that prevent the spindle from forming, and those that stimulate its formation both have anti-cancer activity, any interference with the fine tubulin–microtubule balance prevents normal cell division taking place. Cancer cells are more strongly affected because they are dividing more often and this produces the observed anti-cancer activity.

▼ **Microtubule polymerisation and depolymerisation in the formation and breakdown of the spindle in cell division**

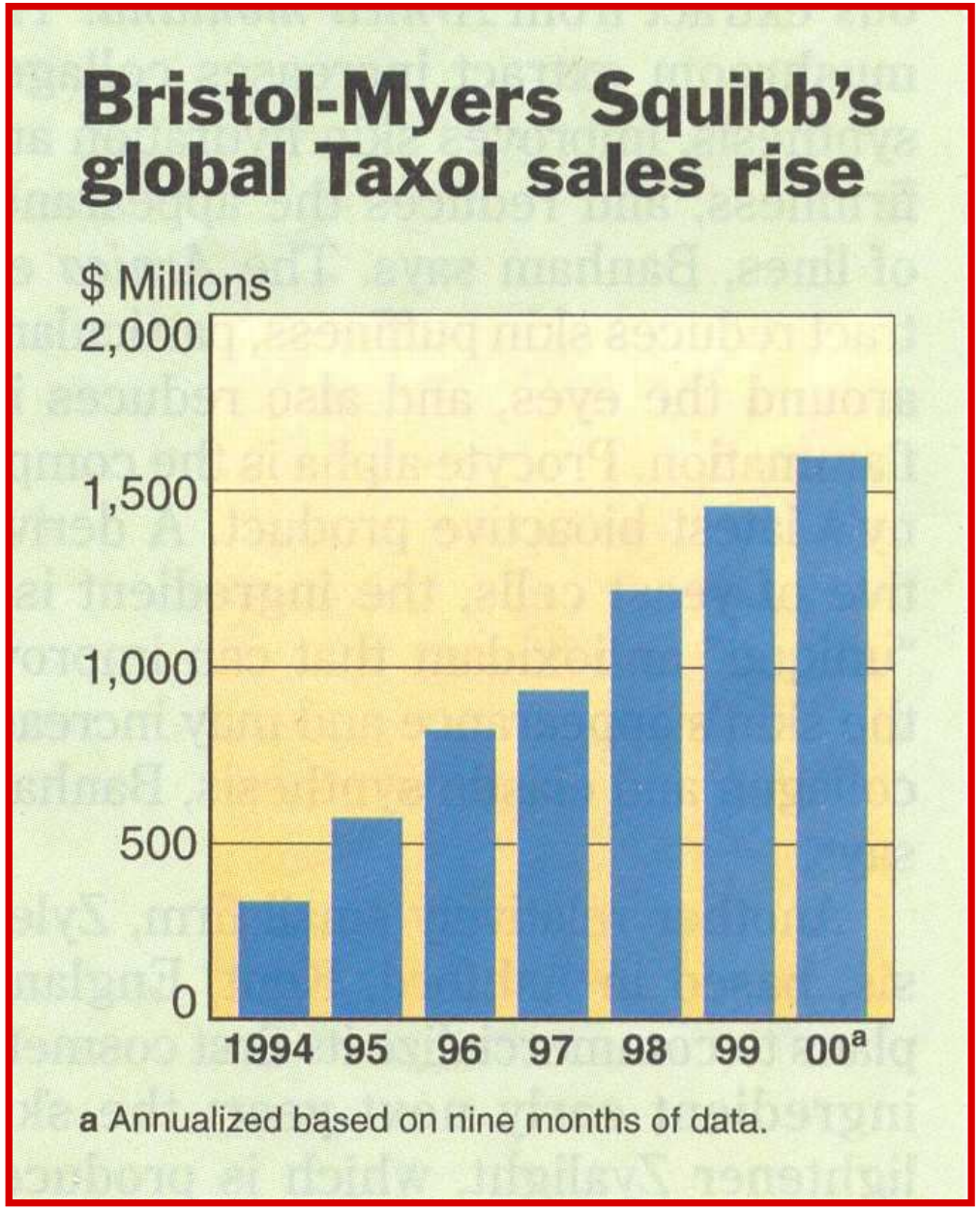

Microtubule depolymerisation
Microtubule polymerisation
Spindle disassembly by microtubule depolymerisation
Spindle assembly by microtubule polymerisation

Common pharmacophore proposed for microtubule-stabilizing agents



Ojima and coworkers propose that two corresponding structural regions (areas colored green and beige) in each of four classes of agents—Taxol, the epothilones, eleutherobin, and discodermolide—account for most of the compounds' antitumor activity. The researchers used nonataxel as a model for Taxol in their study.

C & EN


Bristol-Myers Squibb's global Taxol sales rise
$ Millions
2,000
1,500
1,000
500
0
1994
95
96
97
98
99
00a
a Annualized based on nine months of data.

Paclitaxel path starts with product growth, moves to legal challenges

1963 National Cancer Institute (NCI) finds antitumor activity in yew bark extract.

1971 Active ingredient, paclitaxel, identified.

1979 Paclitaxel mode of action found.

1983 NCI begins Phase I clinical trials.

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1989 NCI looks for commercial development partners.

1991 Bristol-Myers Squibb signs cooperative R&D agreement with NCI.

1992 NCI licenses paclitaxel to Bristol-Myers.

Bristol-Myers' Taxol product approved in U.S. and Canada for treating ovarian cancer.

1993 Bristol-Myers starts developing renewable sources for the drug.

Taxol begins getting approved in Europe, Latin America, and the Pacific Rim.

1994 Taxol approved in U.S. for treating breast cancer.

1995 Semisynthetic form of Taxol receives clearance in U.S.

1997 Taxol approved for AIDS-related Kaposi's sarcoma in U.S. (with seven years of market exclusivity as an orphan drug).

Ivax files for U.S. clearance of Paxene (nongeneric paclitaxel), for Kaposi's sarcoma—final approval depends on expiration of Taxol's orphan drug status.

Bristol-Myers files patent infringement lawsuits against generic drug firms.

1998 Taxol, used with cisplatin, approved in U.S. for ovarian cancer.

Ivax prevails over Bristol-Myers in U.K. patent infringement lawsuit.

Ivax buys Immunex' FDA application, the first filed, on generic paclitaxel.

Annual worldwide sales of Taxol surpass $1 billion.

1999 Taxol/cisplatin approved in U.S. for non-small-cell lung cancer.

Ivax gets European Union approval for Paxene.

2000 Bristol-Myers abandons Taxol patent claims in order to appeal loss against generic producers—case still pending.

Ivax gets tentative approval for generic paclitaxel pending settlement of legal issues between it, Bristol-Myers, and American BioScience Inc. (ABI).

Federal Trade Commission to investigate behavior of Bristol-Myers, ABI, and others in generic drug competition.

ABI continues attempts to block FDA approval, sues Ivax.

Ivax sues Bristol-Myers and ABI for abuse of process, antitrust violations, fraud, and deceptive and unfair trade practices.

Ivax launches generic paclitaxel in October.

PACLITAXEL PATH STARTS WITH PRODUCT GROWTH, MOVES TO LEGAL CHALLENGES

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