

天津大学化工学院系统生物工程
教育部重点实验室 学术报告

NMR of Natural Taxanes

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天然产物在抗肿瘤治疗中起着重要作用

All available anticancer drugs, 1940s-06/2006, by source (N) 175

A 直接来源于天然产物的抗肿瘤药物占14%；B 以天然产物为先导进行全合成或半合成而形成的抗肿瘤药物占51%。
二者共占65%。

"War on Cancer"

Camptothecin
Camptotheca acuminata

Taxol
Taxus brevifolia

1958年美国NCI耗资250亿美元,历时20多年(1958-1980年),对3500余种植物中的11万多个提取物的抗癌活性进行了筛选。

Richard Nixon 1971 "National Cancer"

Taxol® (紫杉醇® 一癌症最后一道防线)

红豆杉: 希望之树

含量 0.004% 1971年
1992年FDA Approved
Ovarian, breast cancers
1994年 \$400 million
2000年 \$1.6 billion

Worldwide Race For Taxol® Synthesis

Holton
Nicolaou
Nature, 1994, 367: 630-634.

Total Synthesis of Taxol®

1971-Present

39 steps 4.3% Holton (1994)
37 steps 0.63% Wender (1997)

39 steps 0.041% Nicolaou (1994)
60 steps 0.17% Mukaiyama (1998)

49 steps 0.63% Danishefsky (1995)
60 steps 0.014% Kawajima (1998)

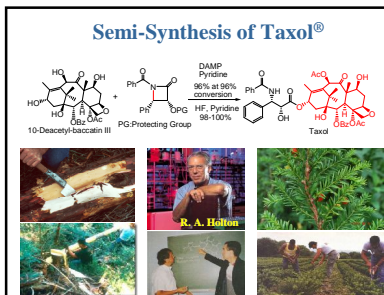
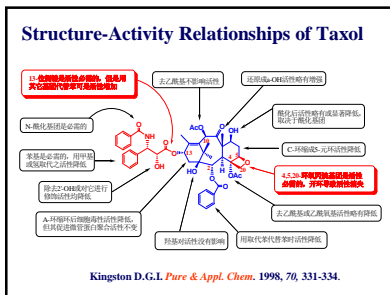
2008年Takahashi (高桥)用了48步收率0.0070%

Timeline of Taxol Research

- ◆ 1966 Isolation of Taxol in a yield of 0.004% from bark of *Taxus brevifolia*.
- ◆ 1971 Establish structure by X-ray and NMR
- ◆ 1977 NCI full-scale preclinical development
- ◆ 1979 Unique mechanism of action was reported.
- ◆ 1981 Phase I clinic trials
- ◆ 1985 Phase II clinic trials
- ◆ 1991 Bristol-Myers Squibb receives CRADA from NCI
- ◆ 1992 FDA approved for drug resistant ovarian cancer.
- ◆ 1994 Total synthesized by Holton and Nicolaou.
- ◆ 1996 Semi-synthesis Taxotere (Docetaxel)

紫杉醇的发明者 Dr. Wall and Dr. Wani

¹H, ¹³C-NMR Spectrum of Taxol®



Nature, An Excellent Synthetic Chemist

红杉 Yew

CO₂ + H₂O

Biosynthesis

紫杉醇 Taxol

Blockbuster Drug: 4 billion \$ in 2006

Distribution of *Taxus* spp

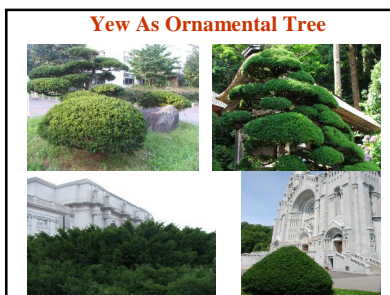
红杉(Yew): 红豆杉科(Taxaceae), 红豆杉属(*Taxus*) 红豆杉科植物。红豆杉属植物全球约11种。拉丁文名称*Taxus*可能源于希腊文字“毒(toxicon)”的意思。红杉是远古第四纪冰川后遗留下来的56种濒危物种植物中最珍稀的药用植物之一, 在地球上已有250万年的历史, 被称为植物王国的“活化石”。

- ### 红豆杉属 *Taxus* spp.
1. 太平洋红豆杉 (Pacific Yew) *Taxus brevifolia*
 2. 欧洲红豆杉 (又称紫果红豆杉) *T. baccata* L.
 3. 墨西哥红豆杉 *T. globosa* Schlechtl
 4. 佛罗里达红豆杉 *T. floridana* Nutt
 5. 加拿大红豆杉 *T. canadensis* March
 6. 喜马拉雅红豆杉 (又称西藏红豆杉) *T. wallichiana*
 7. 云南红豆杉 (又称西南红豆杉) *T. yunnanensis*
 8. 中国红豆杉 (又称红豆杉) *T. chinensis* Rehd
 9. 南方红豆杉 (又称美丽红豆杉) *T. chinensis* var *mairii*
 10. 东北红豆杉 (又称日本红豆杉) *T. cuspidata*
 11. 澳洲红豆杉 *T. sumatrana*

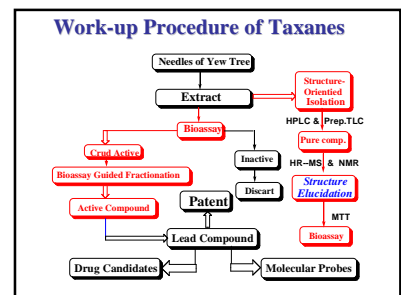
欧洲红豆杉 *Taxus baccata*

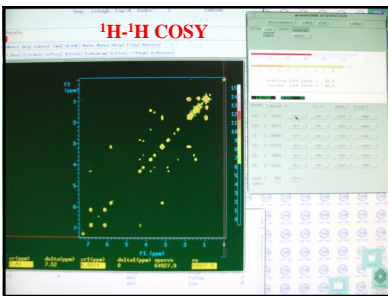
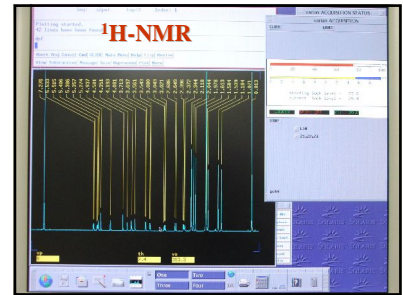
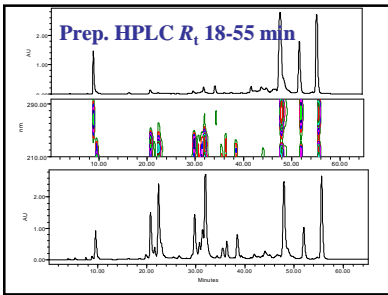
“希望之树”

太平洋红豆杉 *Taxus brevifolia*



加拿大红豆杉和日本产东北红豆杉 *Taxus canadensis* and *T. cuspidata*





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Natural Taxanes: Developments Since 1828

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