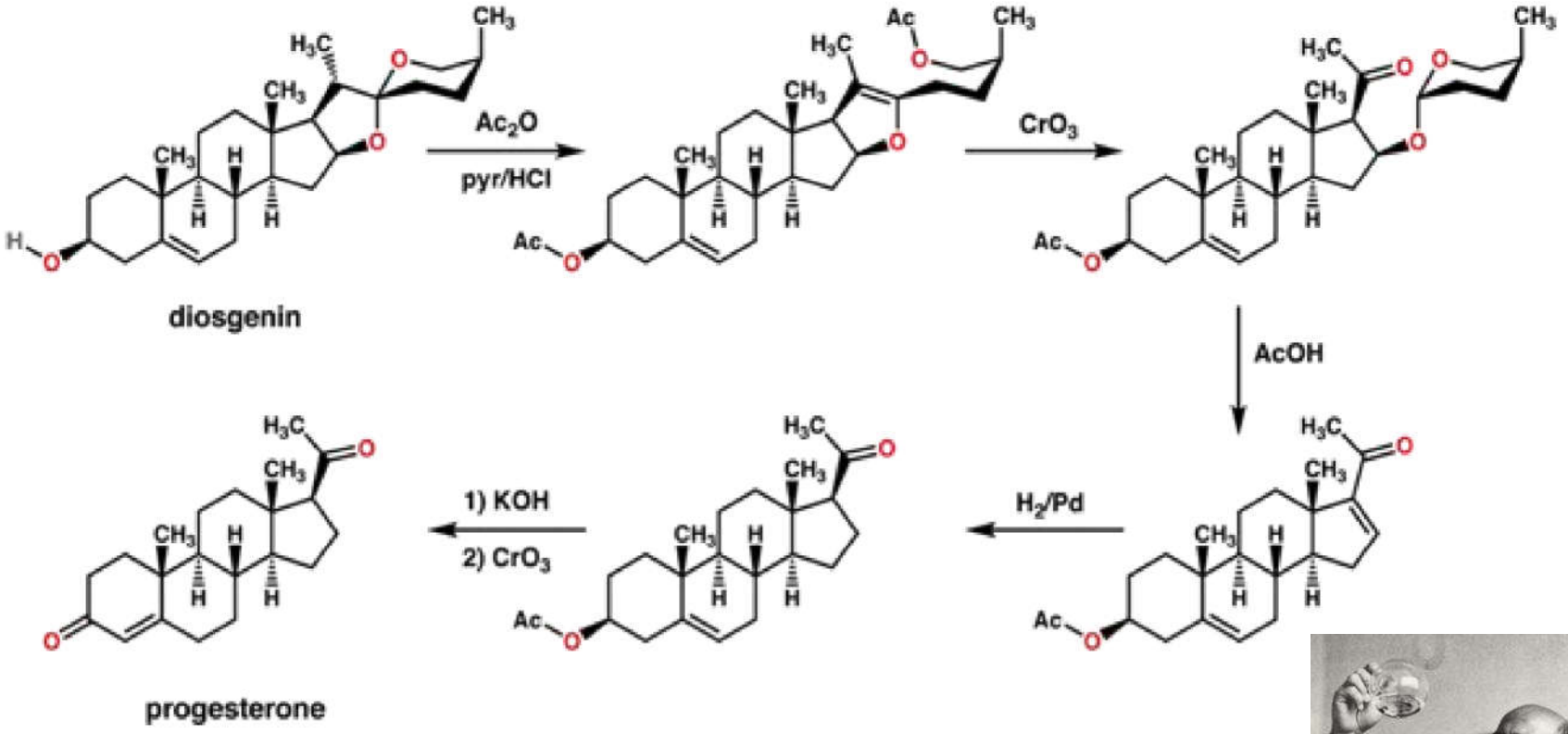
Russell Marker——
Pioneer of the Steroid Hormone Industry



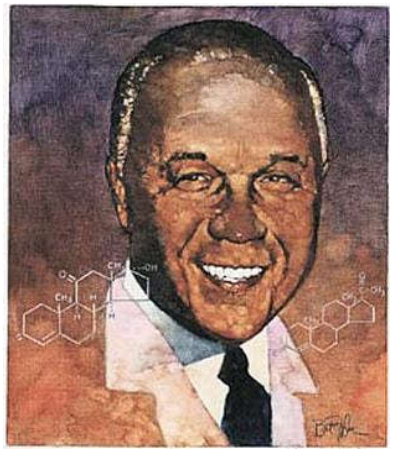
'Marker Degradation'

"Father of the Mexican steroid industry"

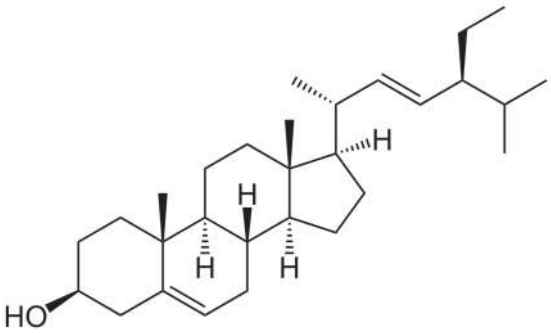
Russell Earl Marker
1902-1995

Dr. Percy Julian

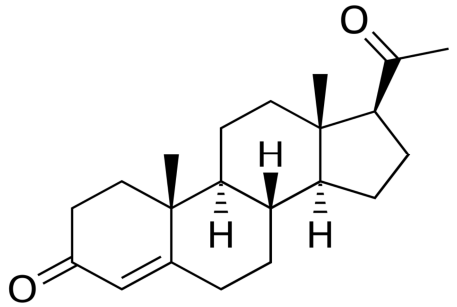
A scientist makes inroads in chemistry and civil rights



African American research chemist and a pioneer in the chemical synthesis of medicinal drugs from plants

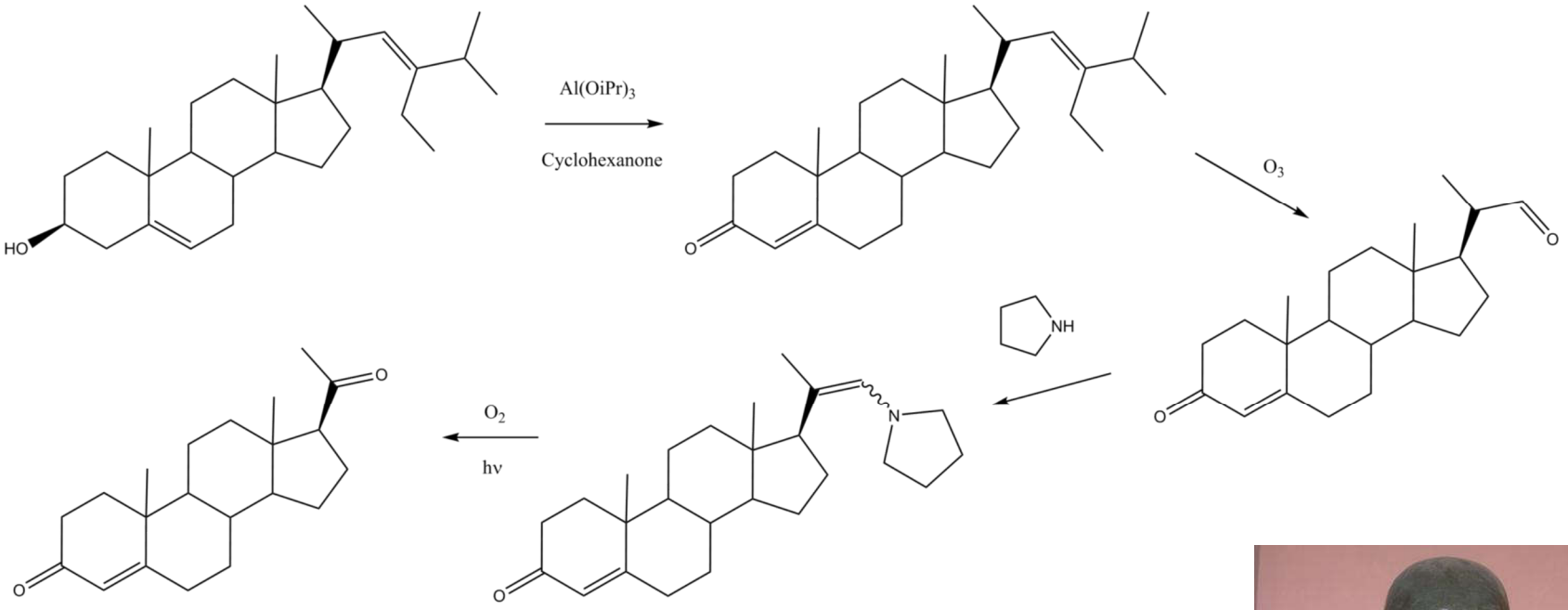


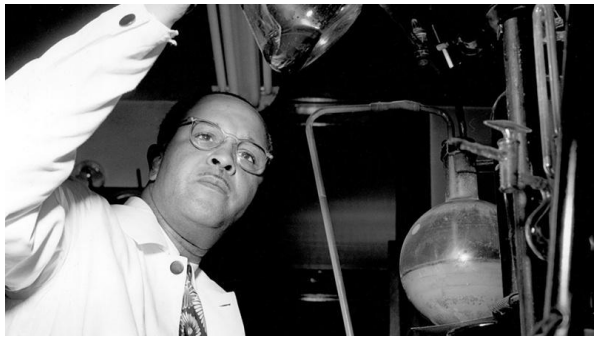
豆固醇 (Stigmasterol)



孕酮 (Progesterone)

Stigmasterol to Progesterone Synthesis

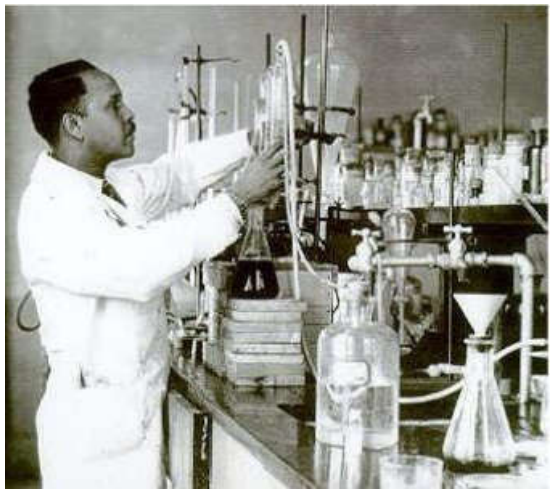




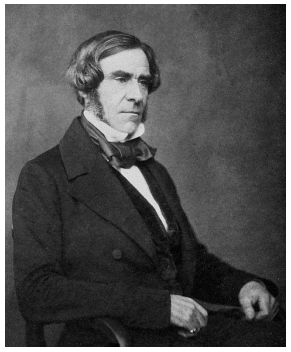
Percy Lavon Julian
A Soybean Chemist

Ernst Späth
(1886-1946)

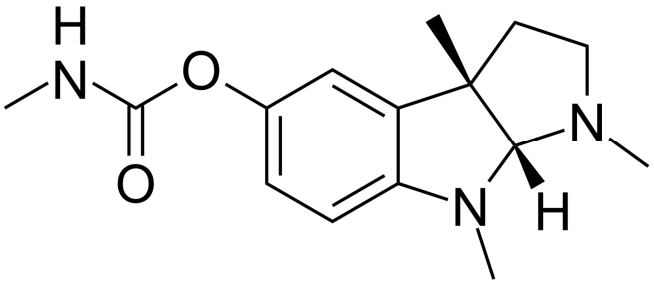
Synthesis of Physostigmine



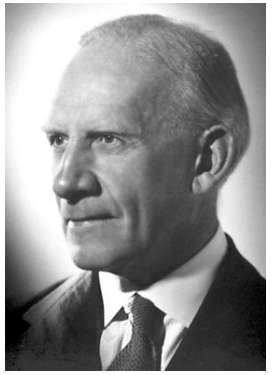
In 1934 at DePauw University Percy Julian synthesized physostigmine from the amino acid, tryptophan.



Sir Robert Christison
(1797 - 1882)
Isolated in 1846



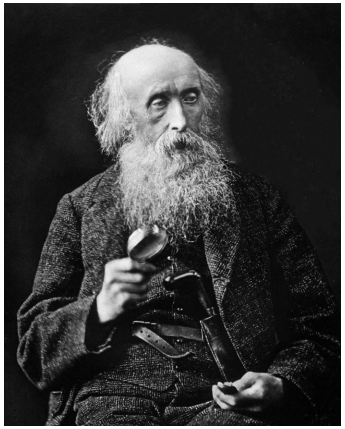
毒扁豆碱 (Physostigmine)



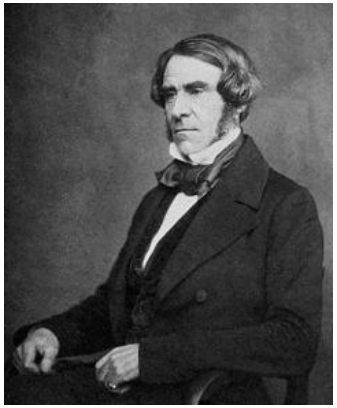
Robert Robinson
(1886-1975)

The killer bean of Calabar

“审判豆”

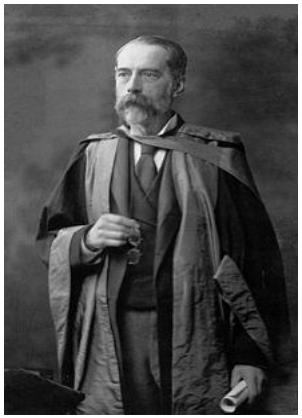


John Hutton Balfour
(1808-1884)
Scottish botanist
Identified Plant i 1861



Robert Christison
(1797-1882)
J. H. Balfour's Student
Isolated Eserine in 1863

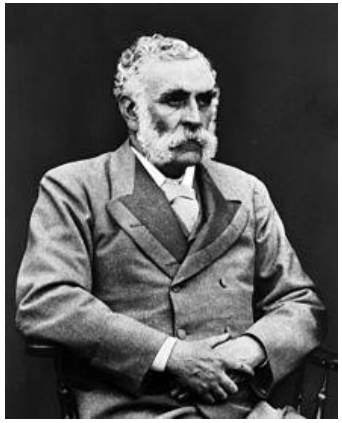
Physostigma venenosum
Calabar bean



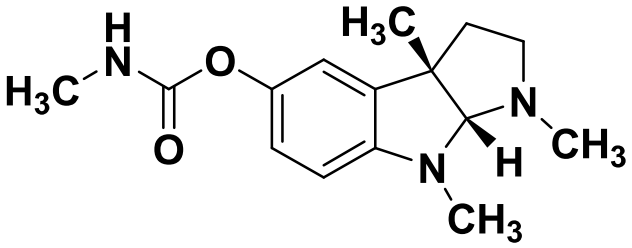
Thomas Richard Fraser
(1841-1920)
R. Christison's Student
Antagonism between physostigmine and atropine

Antagonism Between Curare and Physostigmine
'Physostigmine, an Antidote to Curare'

筒箭毒碱中毒解药



Dr Douglas M. C. L. Argyll Robertson (1837-1909) Introduced physostig mine into ophthalmic practice



Physostigmine 1864, 1925 str.

1875年毒扁豆碱正式应用于防治青光眼引起的失明

1931年合成新斯的明

1934年毒扁豆碱治疗重症肌无力的瘫痪病人获得成功

Otto Loewi (1873-1961)

1920s阐明其作用机制

1936年诺贝尔奖

Mary B. Walker (1888 –1974) Scottish physician

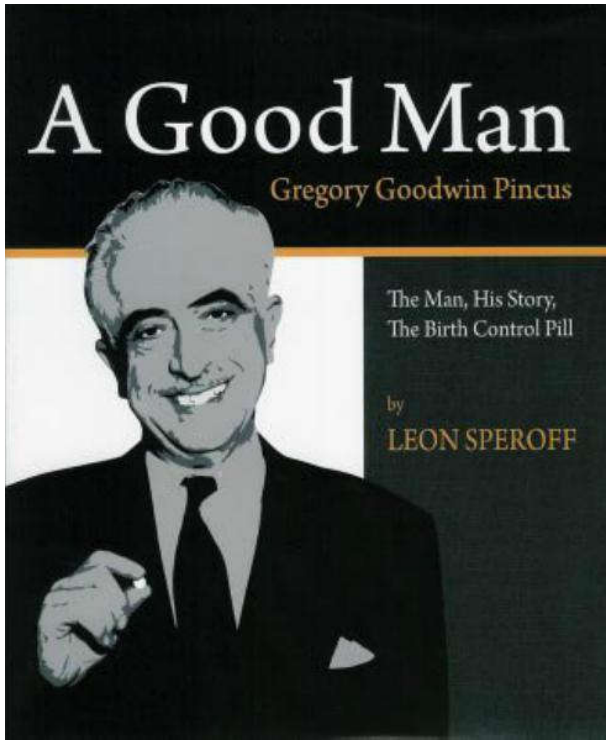
重症肌无力

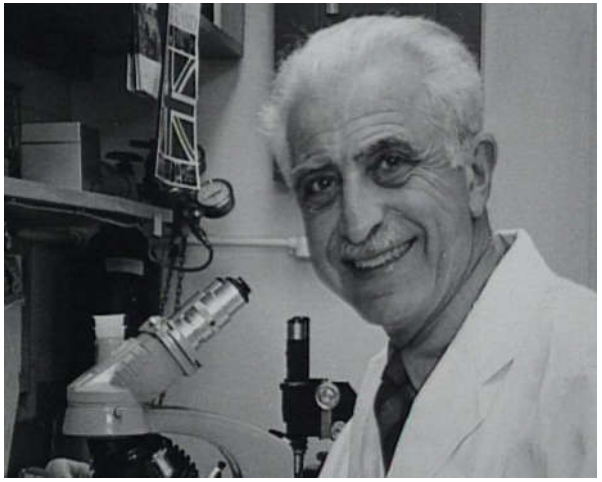
A Historic Discovery in Myasthenia gravis

Father of the Pill—Gregory G. Pincus

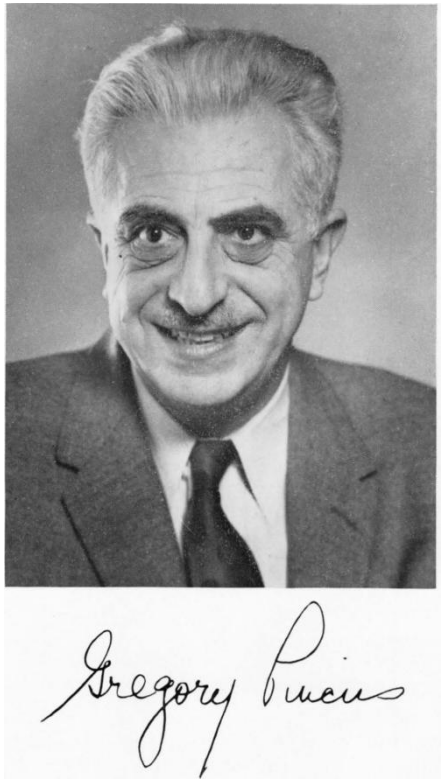
A Good Man-Gregory Goodwin Pincus (1903-1967)

格雷戈里·平卡斯是美国生物学家，他在研制口服避孕药中起了重要作用。在影响人类历史进程的100名人排行榜中排名第82位。





注射孕酮可能会阻止排卵

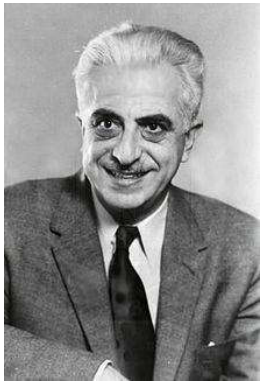


《时代》：美国历史上最具影响力的20大人物

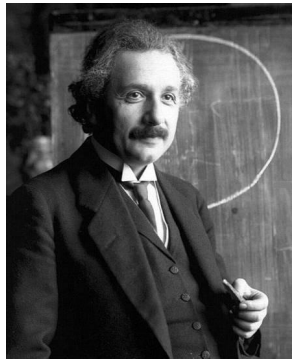
2012年7月26日

一个没有任何政府、企业、大学、基金会资助的研发项目

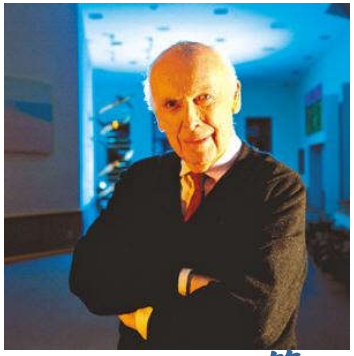
Margaret Sanger第10位



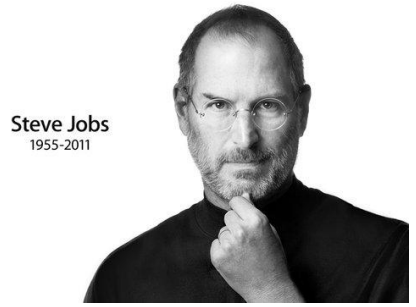
影响人类历史进程的100名人排行榜 格雷戈里·平卡斯列第82位



Albert Einstein第11位

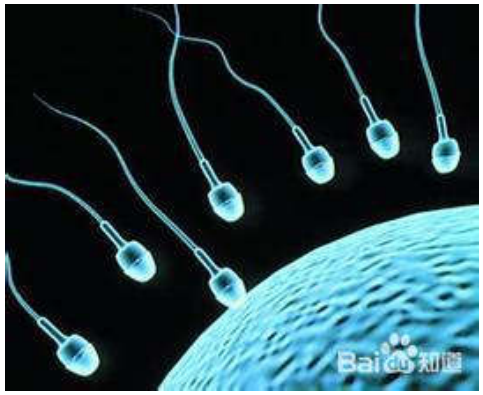


James Watson 第14位



Steve Jobs第17位

Dr. Min Chueh Chang 张明觉

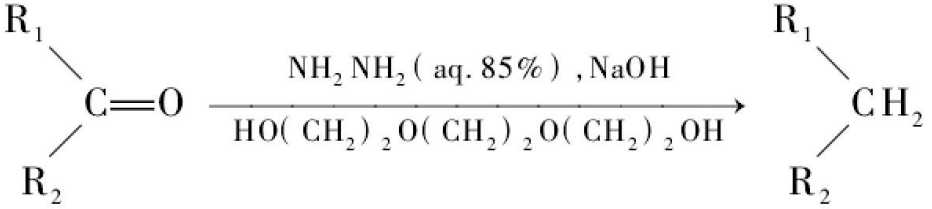


张明觉Chang Min-chueh (1908～1991)

美籍中国生殖生物学家、育种学家和甾体避孕药的创始人之一

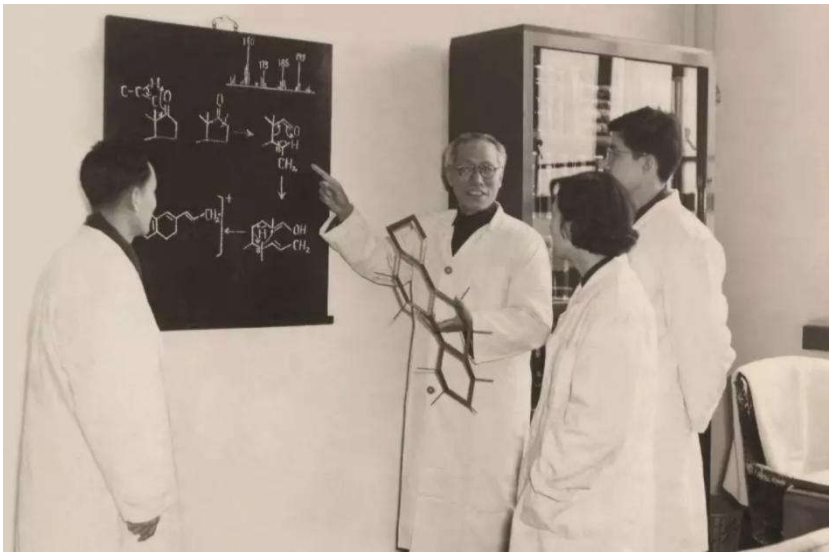
世界上第一例试管婴儿被称为“张明觉的女儿”

黄鸣龙-我国甾体激素药物工业的奠基人

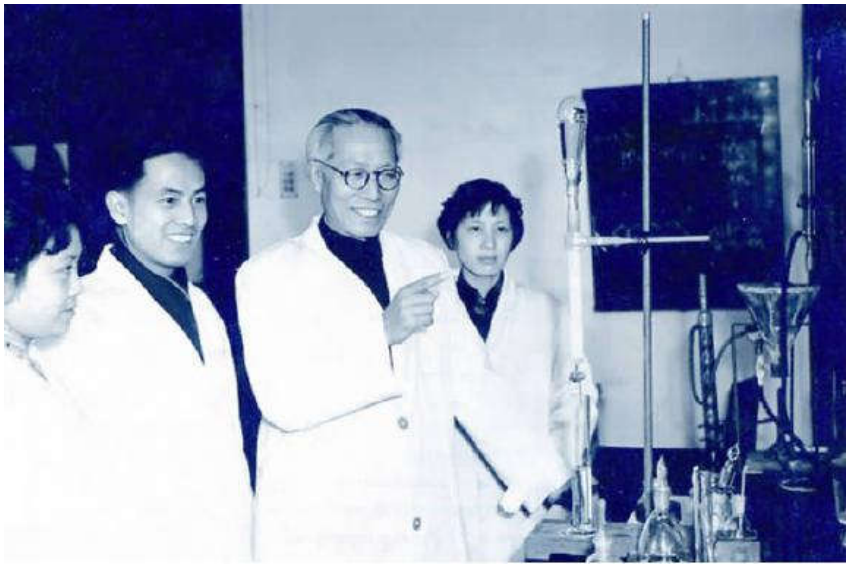


Huang-Minlon Reduction 1946

Louis F. Fieser



1958年在黄鸣龙领导下，以国产薯蓣皂素为原料，合成了“可的松”



1964年，黄鸣龙领导研制的口服避孕药甲地孕酮获得成功

改良的Kishner-Wolff还原法，简称“黄鸣龙还原法”，写入多国有机化学教科书中，并于2002年入选 *J. Am. Chem. Soc.* 创刊125周年被引用最多的125篇论文之一。

Yew Tree: A Tree of Life

红豆杉：希望之树

紫杉醇不仅是科学家打开生命大门的一把钥匙，而且还是医院治疗癌症的一线药物——肿瘤药目录表里第一个抗癌药就是紫杉醇

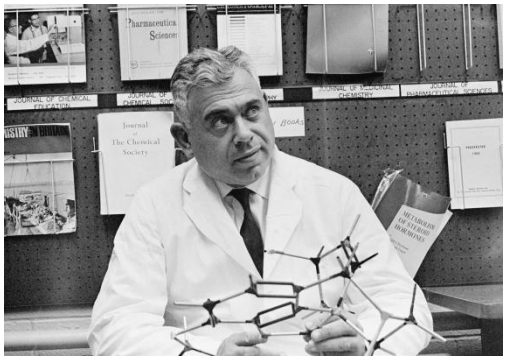
Yew: the Life-giving “Tree of Death”

Tree of Death and Tree of Life?

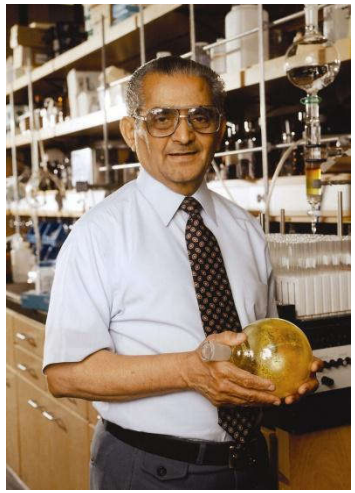
Father-of-three Jonathan Hamilton, 42, took his own life by eating a lethal dose of yew seeds-, 25 Nov. 2008

Finnian Lytle ((right with a friend)), from Brighton, killed himself with a deadly concoction of yew tree poison he gathered from his garden, an inquest heard today. 24 August 2017 Daily Mail

The National Historic Chemical Landmarks



Dr. Monroe E. Wall



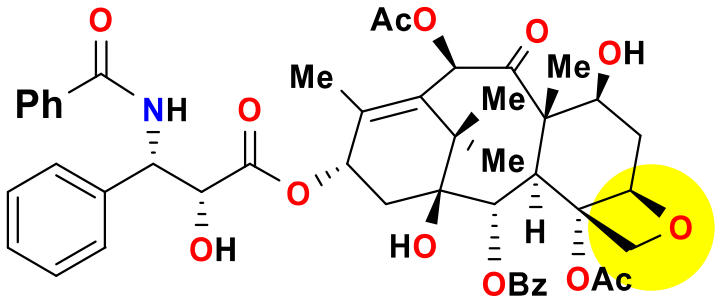
Dr. Mansukh C. Wani

紫杉醇的发现者Wani博士和Wall博士

Dr. Andrew T. Mcphail, Duck Uni. X-ray，被引用次数：5047

Mechanism of Taxol®

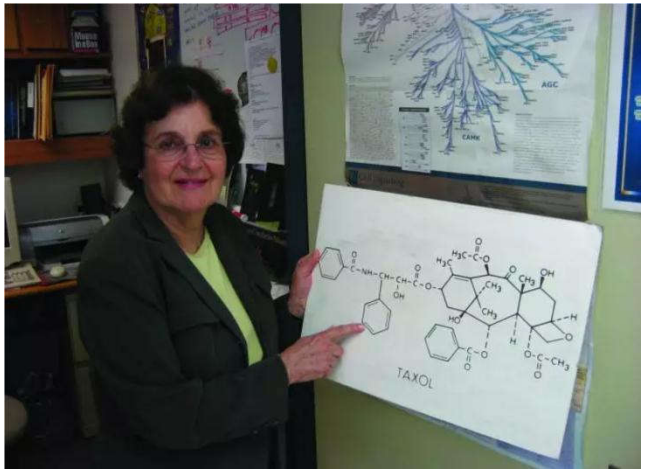
The timing was fortuitous—Susan Horwitz's groundbreaking discoveries about Taxol helped make it a blockbuster drug

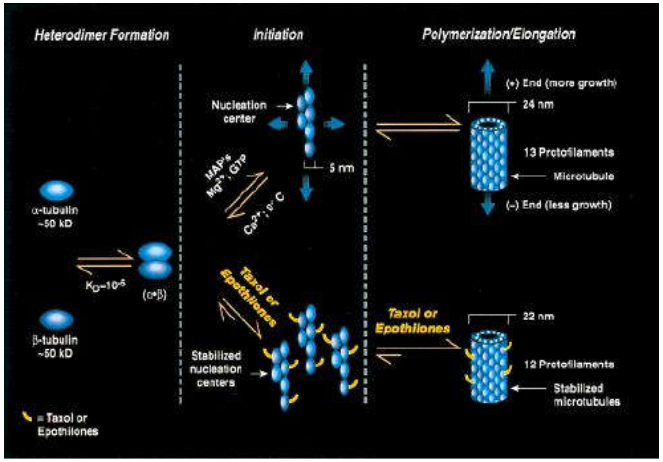


0.004%

"A structure that only a tree could make"

Dr. Peter B. Schiff and Dr. Horwitz





Susan Band Horwitz, 2019年盖尔德纳国际奖获得者

Nature 1979, *277*: 665-667

被引用次数：4210

紫杉醇——明星分子

Taxol is not as taxing
Thank Goodness!

Arthur Barclay, USDA
First bark collection, 1962

Ross Longley and Steven Schmid for pharmacology

Mansukh Wani ,
Monroe Wall
Research Triangle Institute
Isolation from bark of *T. brevifolia* 1971

Susan Horwitz
Albert Einstein School of Med.
Unique MOA 1979

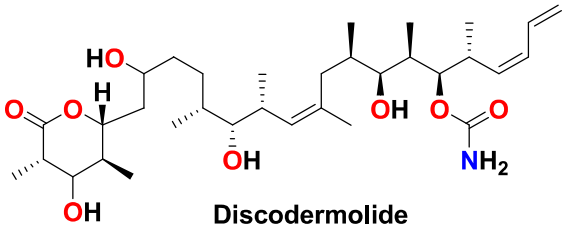
Peter Wiernik, Our Lady of Mercy Med. Center.
Pioneered slow infusion. 1983

Pierre Potier, CNRS, France.
Pioneered semisynthesis from 10-deacetyl baccatin isolated from leaves of *T. baccata*. 1988

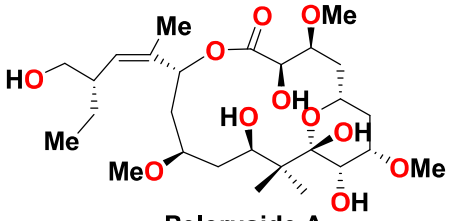
Eric Rowinsky
Johns Hopkins U.
Efficacy in refractory ovarian cancer. 1989

Microtubule-stabilizing Agents from Nature

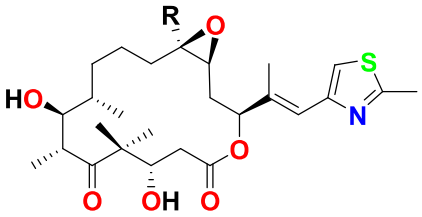
Nature 1979, *277*: 665-667



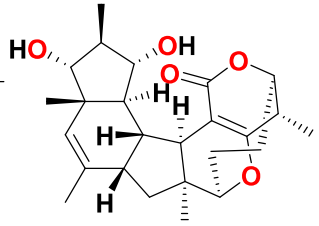
Discodermolide



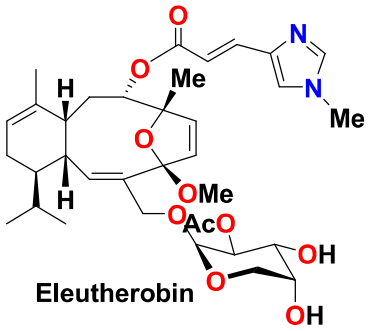
Peloruside A



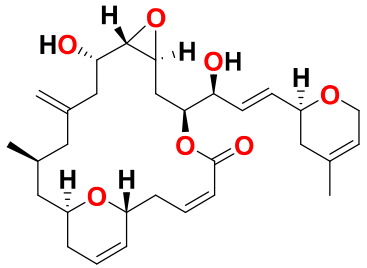
Epothilone A R=H
Epothilone B R=CH_3



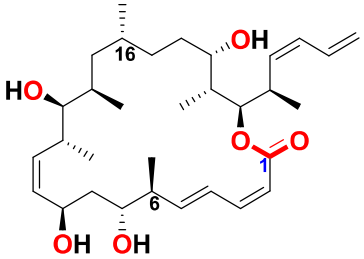
FR182877



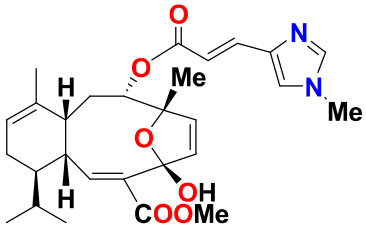
Eleutherobin



Laulimalide



Dictyostatin



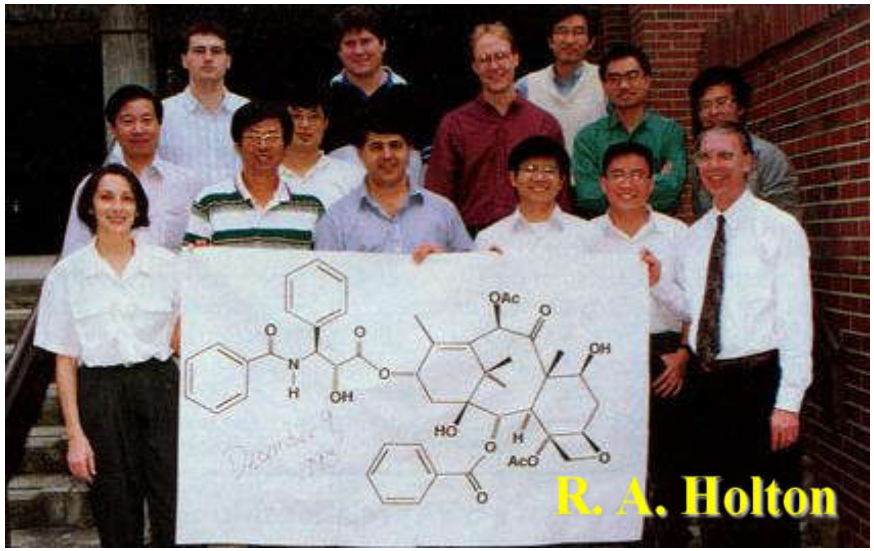
Sarcodictyin A

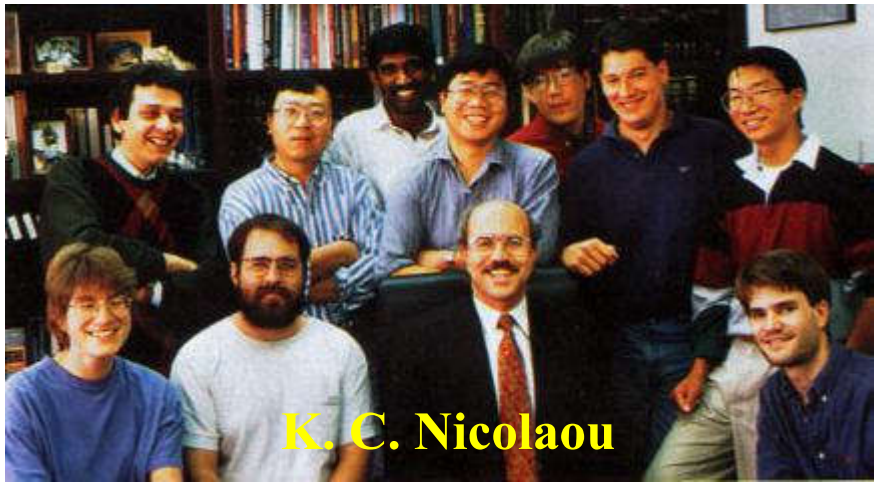
Horwitz in the laboratory.

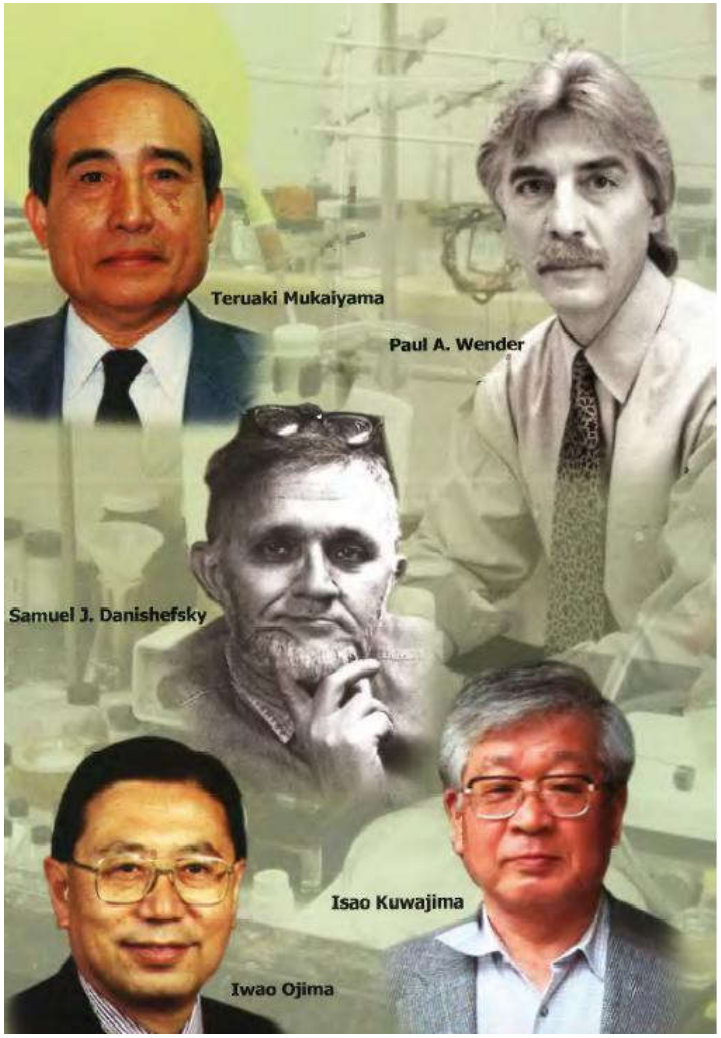
Her landmark research would help turn the molecule into one of the world's most effective anti-cancer blockbuster drugs.

Worldwide Race For Taxol® Synthesis

世界最难合成-Taxol---till 22 years after its complete structural elucidation.

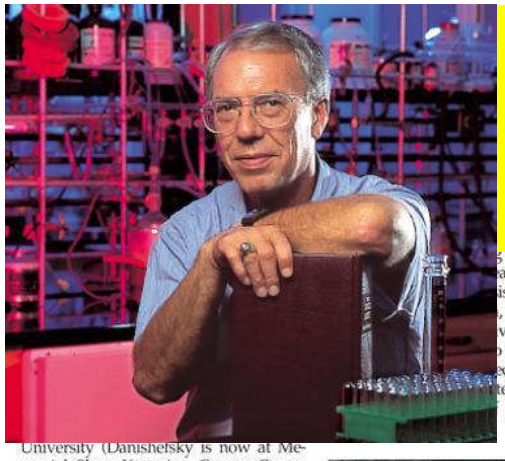


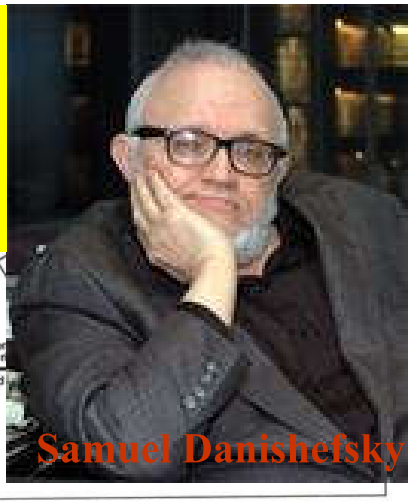




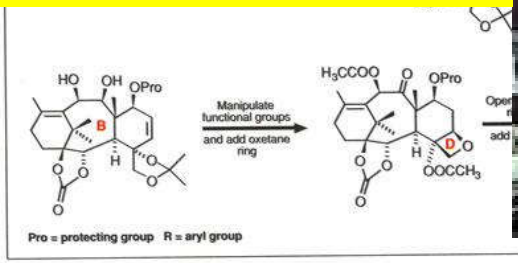
Nature, 1994, *367*: 630-634.

Race to Synthesize Taxol Ends in A Tie—Science 1994





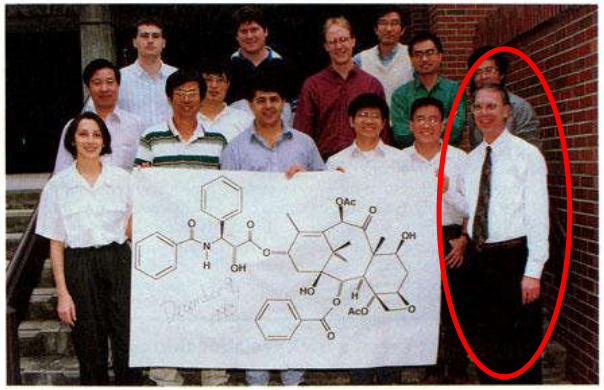
Samuel Danishefsky

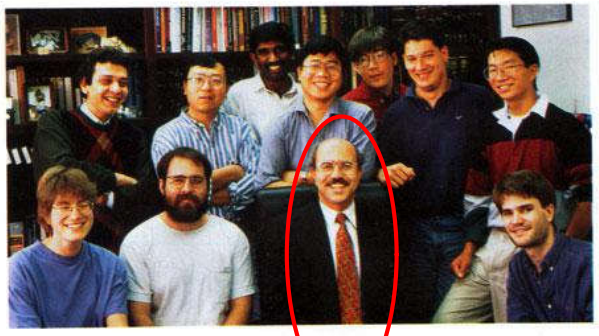


University (Danishefsky is now at Memorial Sloan-Kettering Cancer Center and Columbia University).

After the oxetane is added, Holton and coworkers complete the synthesis by adding taxol's side chain to ring A—using a technique developed and patented by Holton and now used by

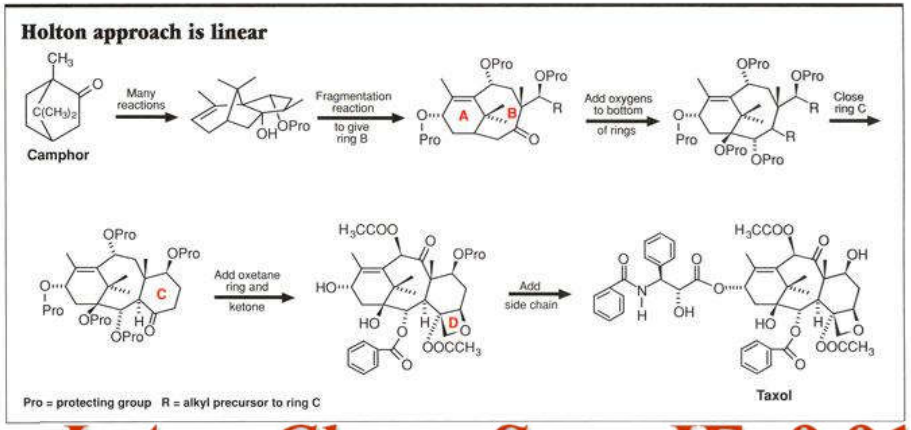
Florida State University taxol team includes (front row, from left) postdoctoral fellows Carmen Somoza, Hyeong-Baik Kim, Hossain Nadizadeh, and Chunlin Tao, graduate student Phong Vu, and chemistry professor Robert Holton; (middle row, from left) postdoctoral fellow Pingsheng Zhang, graduate student Chien-Tai Ren, postdoctoral fellow P. Douglas Boatman, graduate student Feng Liang, and postdoctoral fellow Suhan Tang; and (back row, from left) graduate student Chase C. Smith and postdoctoral fellows Ronald J. Biediger and Yukio Suzuki.

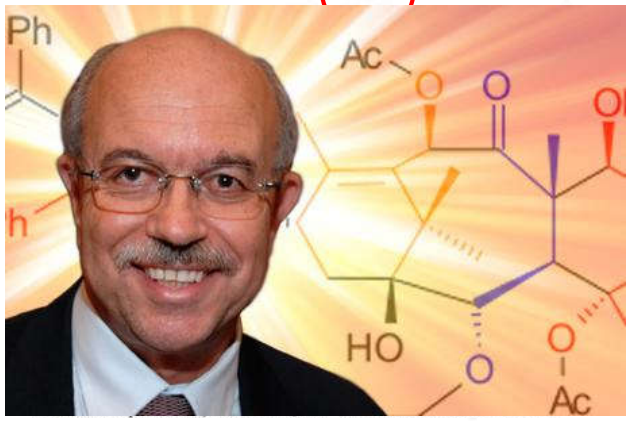




Taxol group at Scripps and UCSD includes (standing, from left) visiting scientist Elias A. Couladouros, postdoctoral fellows Jin-Jun Liu, K. Paulvannan, and Zhen Yang, graduate student Erik J. Sorensen, postdoctoral fellow Philippe G. Nantermet, and visiting scientist Hiroaki Ueno; and (seated, from left) postdoctoral fellow Johanne Renaud, graduate student R. Kip Guy, professor K. C. Nicolaou, and graduate student Chris F. Claiborne. All are at Scripps, except Sorensen, who is at UCSD. Nicolaou has a joint appointment at Scripps and UCSD.

"The achievement is an academic one at the moment," says Nicolaou, "but it could eventually pave the way to a more practical synthesis. We feel the main advance lies in our ability to construct designed taxols that have better biological



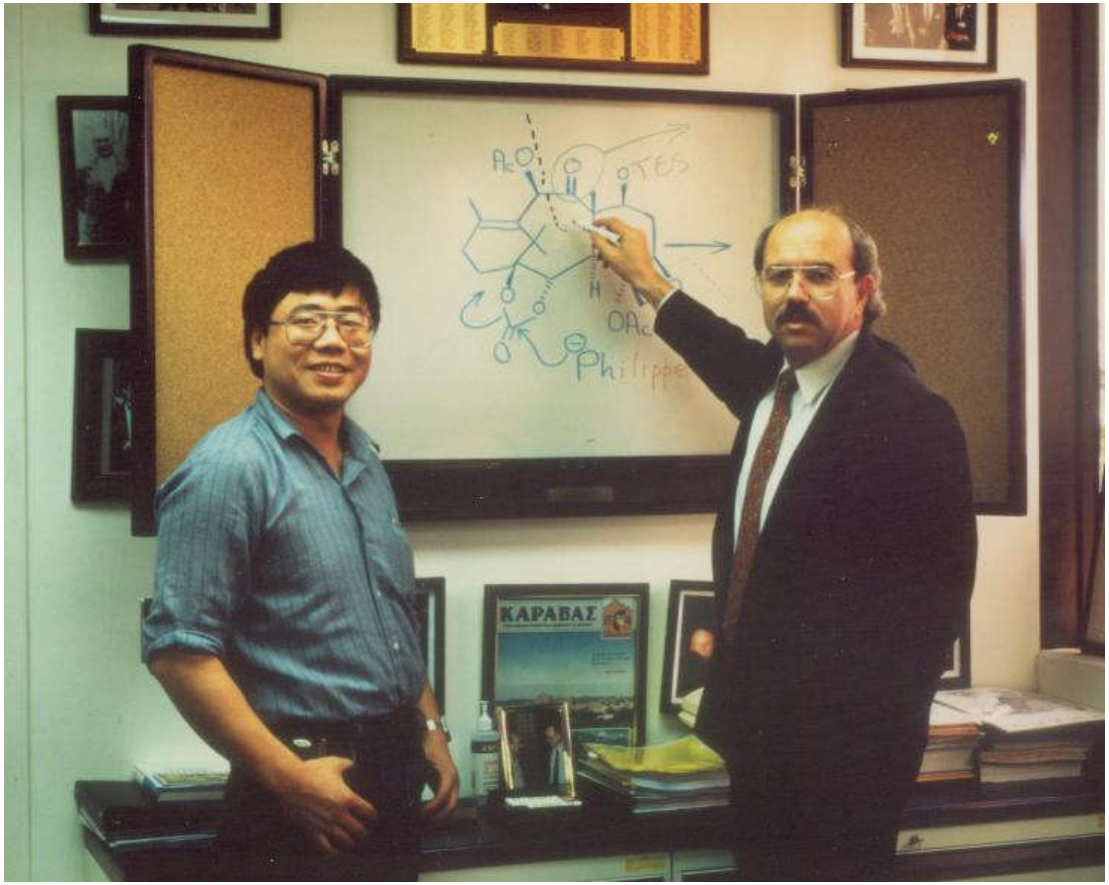


34 FEBRUARY 21, 1994 C&EN

J. Am. Chem. Soc., IF=9.91
1994, *116*: 1597-1598. 引用688

Nature, 1994, *367*: 630-634. 杨震
IF = 36.28 引用856

杨震 教授



杨震 教授与K. C. Nicolaou教授，外号KCN(氰化钾)

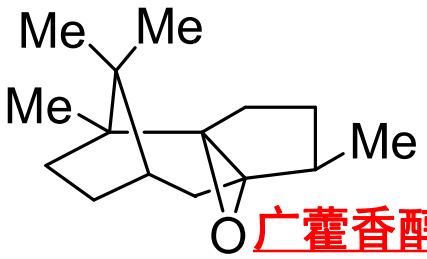
黄乃正 院士

E. J. Corey

R.Woodward

Total Synthesis of Taxol-"A molecular Mount Everest"

More than 100 academic groups worldwide were working on it



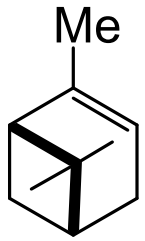
广藿香醇

+16

39 steps

4.3%

Holton (1994)



蒎烯

37 steps

0.63%

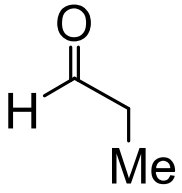
Wender (1997)

黏酸

39 steps

0.041%

Nicolaou (1994)

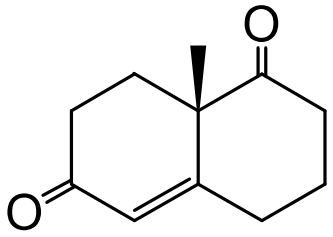


合成构素

60 steps

0.17%

Mukaiyama (1998)

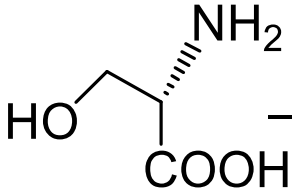


维兰德-米舍尔酮

49 steps

0.63%

Danishefsky (1995)



丝氨酸

60 steps

0.014%

Kuwajima (1998)

2008年Takahashi (高桥)用了48步收率0.0070%

Total Synthesis of Taxol

Nicolaou team (1994)

51 steps
0.03% yield

Wender team (1996)

37 steps
0.2% yield

Danishefsky team (1995)

41 steps
2% yield

47 steps
0.2% yield

Holton team (1994)

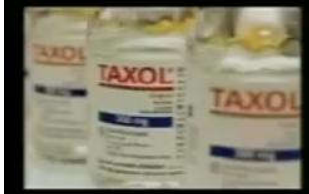
1:02:33 / 1:11:27

Sustainable Supply of Taxol

European yew (*Taxus baccata*)
3000 kg needles for 1 kg precursor
renewable biomass

10-deacetylbaccatin III

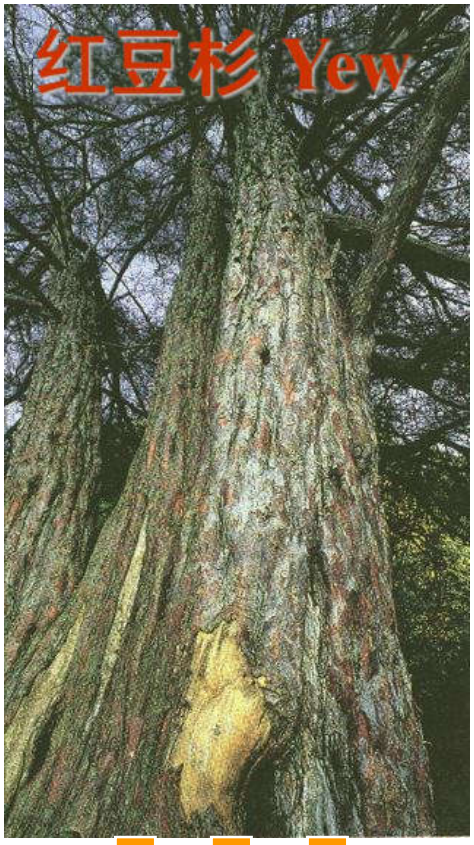
semi-synthesis *4 steps*



Treat cancers:
- ovarian
- breast
- lung
- pancreatic

- 1992: approved by FDA
- 2001: world's top-selling anticancer drug
- $2 billion sales (BMS)

Nature, An Excellent Synthetic Chemist

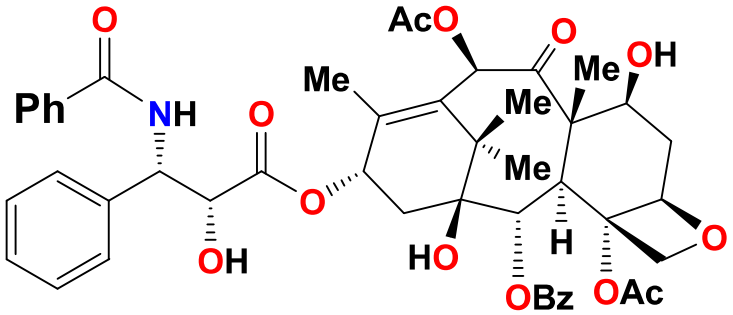


$CO_2 + H_2O$

hυ

光合作用–世界上最伟大的反应

Nat. Prod. Chem.



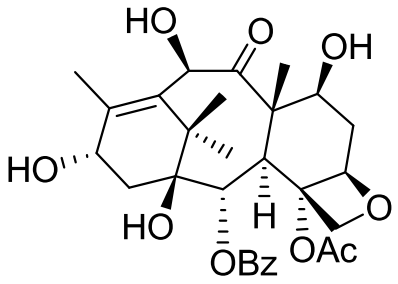
紫杉醇 Taxol

世界最难合成小分子

$ $ $ $

Blockbuster Drug: 10 billion $ in 2000

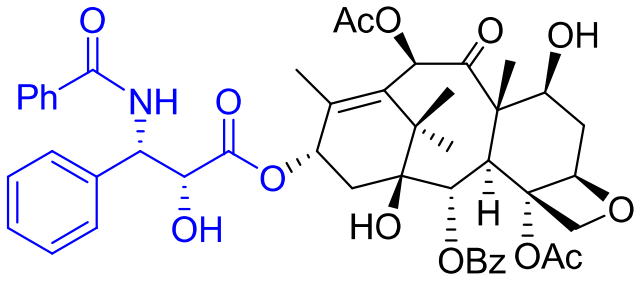
法国“化学之家”主席Pierre Potier



10-Deacetyl-baccatin III

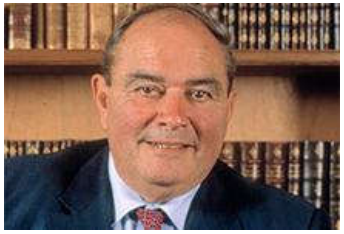
1988

1981



Taxol

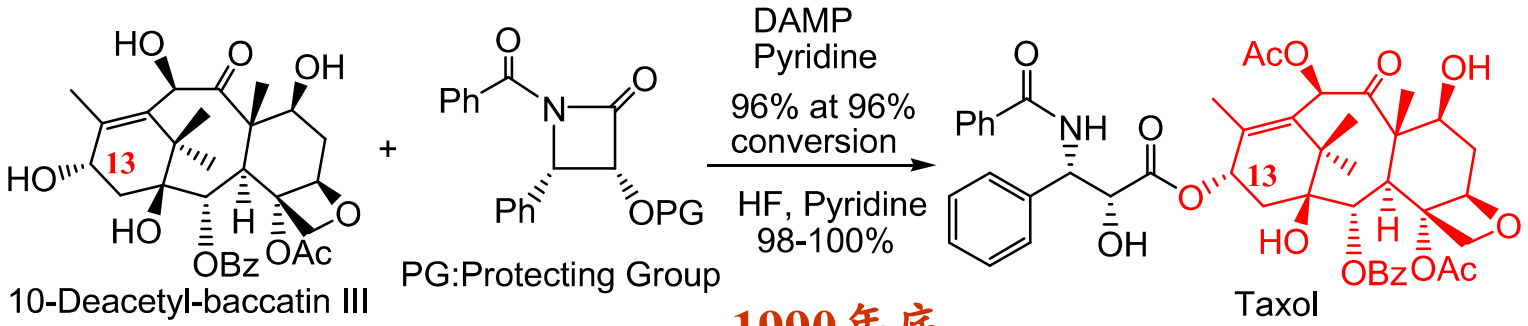
总产率50%



Pierre Potier
(1934-2006)

Pierre Potier教授也是中法科技交流的先驱者，1976、80年应我国政府邀请访问中国

Largest pay-offs and Richest Prof. Holton

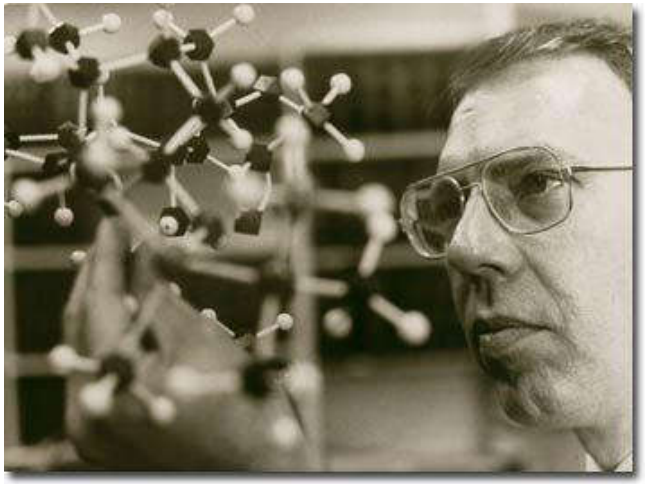


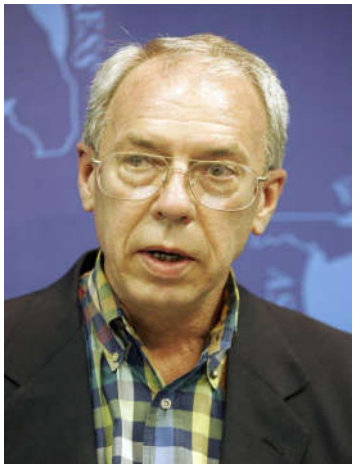
10-Deacetyl-baccatin III

PG:Protecting Group

Taxol

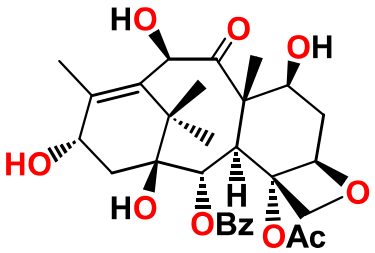
1990年底





Taxol —the world's best-selling anti-cancer drug by 1994, generating world-wide sales approaching $10 billion by 2000. Holton's work generated around $351,000,000 for the university, which is still the largest income royalty ever generated by a university-licensed technology in the United States.

Semi-synthesis of Taxol

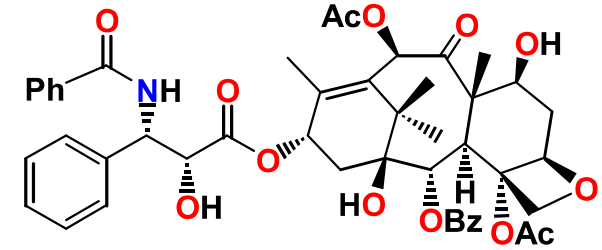


10-deacetylbaccatin III

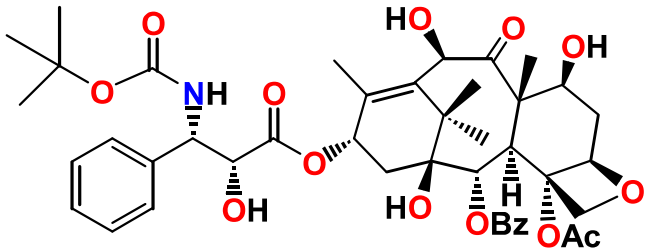
含量可达0.1%

Semisynthesis

1988



Paclitaxel (Taxol)

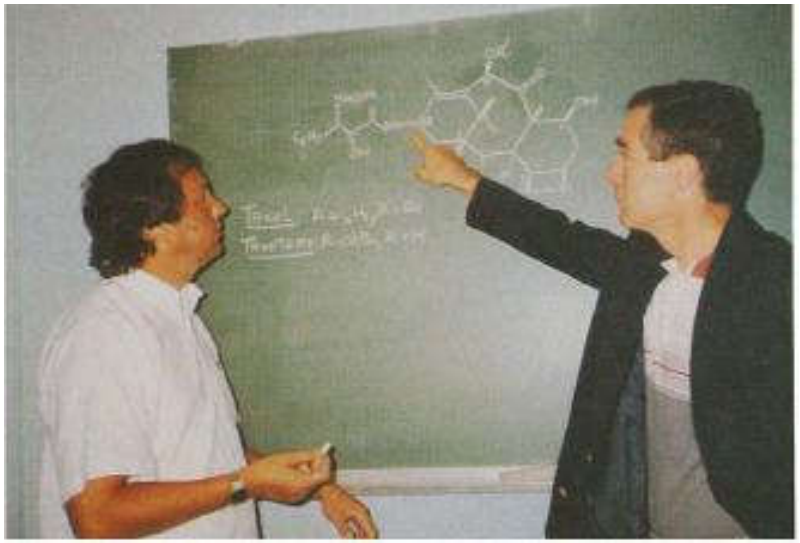


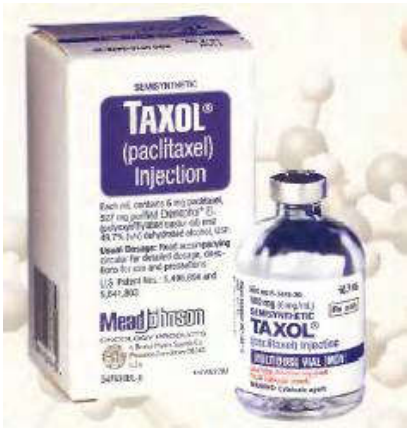
Docetaxel (Taxetere)

活性是紫杉醇2.7倍

1995 FDA

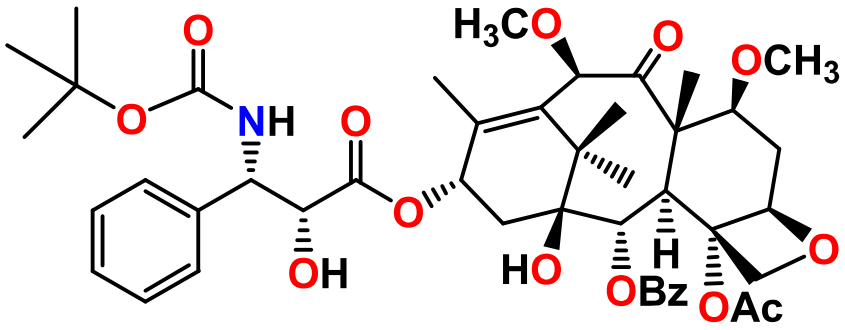
Dr. Pierre Potier and Andrew Greene



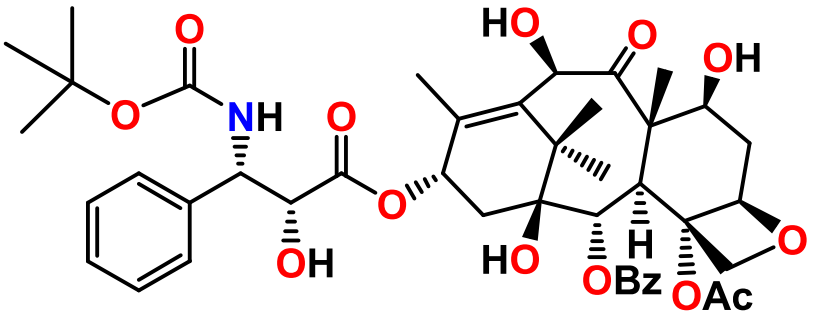


European Yew

Semi-synthesis of Taxol



Cabazitaxel (卡巴他赛)



Docetaxel (多烯他赛)

Cabazitaxel was developed by Sanofi-Aventis and was approved by FDA for the treatment of hormone-refractory prostate cancer on June 17, 2010.

NATURE|Vol 440|16 March 2006 NEWS & VIEWS

OBITUARY

Pierre Potier (1934–2006)

Pharmacist and natural-products chemist, who devised widely used treatments for cancer.

Pierre Potier, who died on 3 February 2006 at the age of 71, was at the forefront of the French school of natural-products chemistry during the second half of the twentieth century. He was a leading light in the development of anticancer drugs from natural sources, and also in encouraging communication between the public and private sectors. In France, these circles tend not to mix. Potier showed that cooperation between the CNRS, the main agency of publicly funded research, and industry could be highly fruitful if the two communities shared their knowledge and experience

identify the anticancer activity of vinorelbine (Navelbine), a semi-synthetic derivative of the vinca alkaloids vincristine and vinblastine found in periwinkles. All three drugs inhibit cell division, and have been part of anticancer treatments since the mid-1970s. The production of vinorelbine was taken up by the Pierre Fabre Laboratories for use in treating lung cancer and breast cancer in particular. (Poignantly, Potier's first wife Marie-France, herself a pharmacist, had died of breast cancer in 1968. Potier remarried, and is survived by his second wife Odette and three children.)

JOURNAL OF NATURAL PRODUCTS

Editorial

Cite This: J. Nat. Prod. 2018, 81, 449−450

pubs.acs.org/jnp

Special Issue in Honor of Professor Susan Band Horwitz

It is with great pleasure and admiration that we as Guest Editors present this special issue of the *Journal of Natural Products* honoring the significant accomplishments of Dr. Susan Band Horwitz of the Department of Molecular Pharmacology

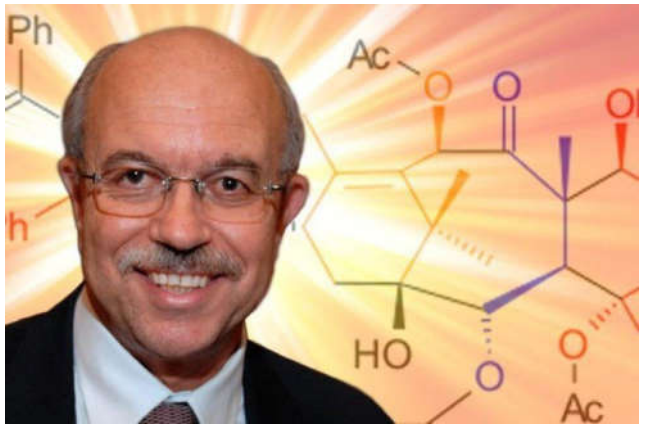
a distinct mechanism of action, and her discovery of its unique mechanism of action was groundbreaking.[11,12] Numerous antimitotic natural products had been identified prior to the isolation of taxol, and plant-derived compounds including colchicine and the vinca alkaloids were instrumental in identifying tubulin as a drug target, but each of these early tubulin-binding compounds were microtubule depolymerizers, which inhibit tubulin polymerization and cause the loss of cellular microtubules. Elegant studies by Dr. Horwitz and her students in sequential papers in *Nature* and *Proc. Natl. Acad. Sci. U.S.A.* highlighted the unique microtubule-stabilizing effects of taxol.[11,12] These studies demonstrated that it stimulated the polymerization of purified tubulin, stabilized tubulin polymers from cold or calcium-induced depolymerization, and caused the formation of unique microtubule bundles in cells. Taxol was found to be a potent cytotoxin and caused mitotic arrest and bundled microtubules that were resistant to cold and depolymerization by steganacin. A new class of microtubule-binding drugs was thus identified and provided strong additional justification for the National Cancer Institute to continue the clinical

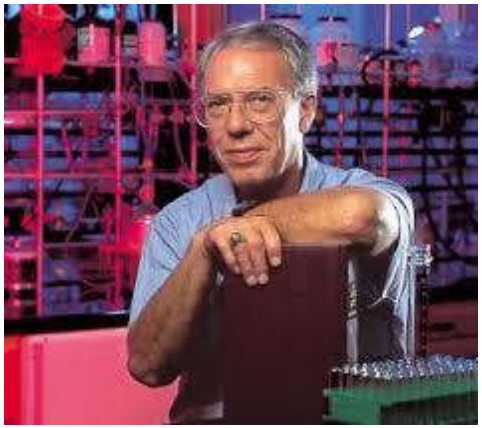
Editorial

Special Issue for Monroe Wall and Mansukh Wani

Figure 1. Dr. Monroe Wall (left) and Dr. Mansukh Wani (right). Photographs by John H. Theilgard (Research Triangle Institute).

The Charm and Appeal of Taxol

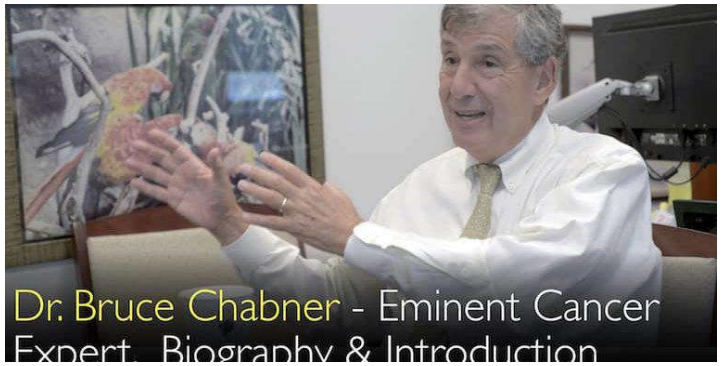




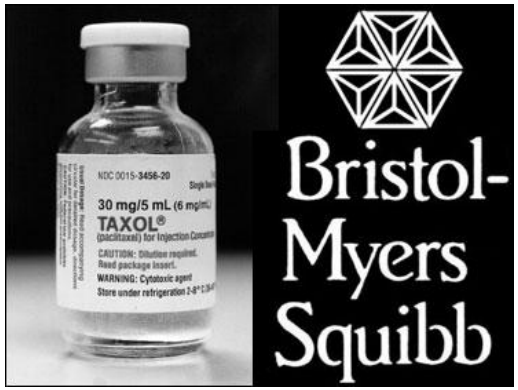
Kyriacos Costa Nicolaou

Robert A.Holton

The Clinical Development of Paclitaxel: A Successful Collaboration of Academia, Industry and the National Cancer Institute



Dr. Bruce Chabner – Eminent Cancer Expert and Direct of NCI



Dr. Eddie Reed Chief of the clinical development of Taxol

A Long Road from Labs to FDA Approve

Taxotere or Taxol – Which one is better?

Newer studies that compared the safety and effectiveness of the two taxanes found that Taxotere isn't better than Bristol-Myers Squibb's older medication, but it was, in fact, more dangerous.

方起程研究员与紫素注射液

1987-1988年 任美国三角研究所访问学者和顾问。1995年分别获得卫生部颁发的新药证书。用于治疗转移性卵巢癌、乳腺癌以及食管癌和肺癌等。1996年被评为国家级新产品。1996年和1997年先后获卫生部科技进步一等奖和国家科技进步三等奖（第一完成人）

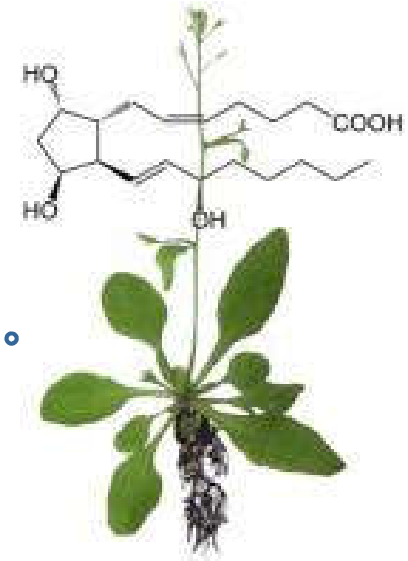
天然药物化学

一个充满魅力的领域

- Integrated development of Natural Product Chemistry with Molecular Biology and Biochemistry.
- Exploration of secondary metabolites of organisms hold promise for new Natural Products that may improve our health and our lives.

Bottleneck

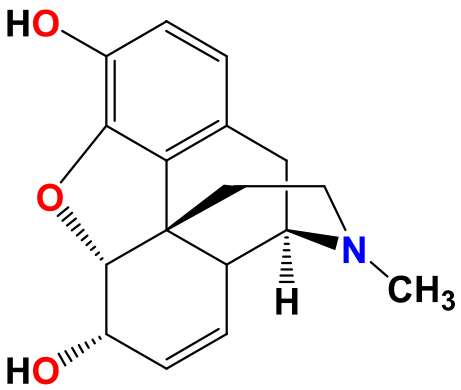
1. 分离得到的化合物量少，以毫克计。
2. 很多活性筛选仅仅停留在MTT抗肿瘤细胞粗筛。
3. 目前大部分只能以化合物的形式发表，没专利不能开发。



大自然的影响无处不在，天然产物化学的成果遍布我们生活的各个角落，我们必须努力细心地寻找。

吗啡 (Morphine)：天然药物化学的开端

Morphine: An 8000-year Journey



Morphine 1805

Alkaloid chemistry

Pium
(poppy tears)

"God's own medicine"

Friedrich Sertürner
(1783-1841)
A amateur scientist
Heroes of Pharmacy Safety

背景：1803年J. Dalton提出Atomic Theory; 1805年J. Gay-Lussac证明了水是H_2O
1807年贝采利乌斯"生命力"学说正式诞生

结论1：植物之中不只是有酸性物质，还有碱性物质

结论2：植物之中的化学物质是可以分离的　　not "power of life"

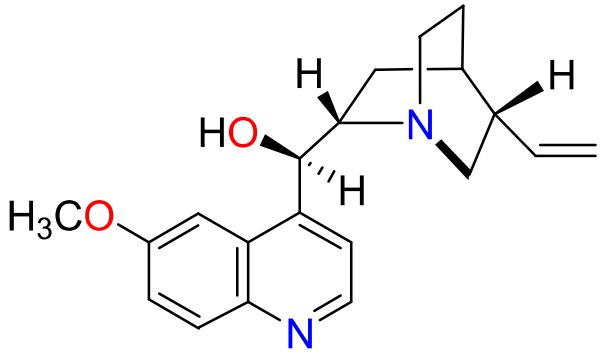
结论3：植物药起作用的不是植物本身，而是其中所含有的化学成分

结论4：促进了生物碱化学和天然药物化学的形成和药理学成为一独立学科

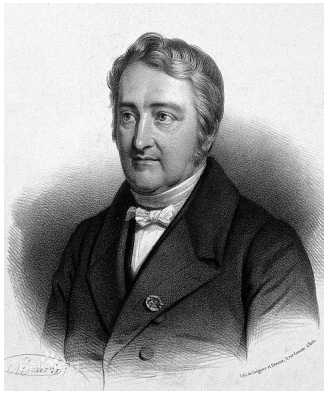
奎 宁 Quinine

一个意外成就一个翻天覆地的发现

Joseph B. Caventou
(1795-1877)



Quinine 1820
From Fever tree to Countess's powder to Quinine
solved the mystery of "cinchona bark"



Pierre Pelletier
1788-1842

背景： 贝采利乌斯： 1806年提出“有机化学”的概念；1807年提出“生命力”学说；1813年创建了世界性化学语言-元素符号

Conclusion 1：Significantly influenced the transformation of pharmaceutical chemistry from a state of alchemistry to an acknowledged branch of science

Conclusion 2：Promoted development of pharmaceutical science and pharmaceutical industry

Pharmacology & Forensic Toxicology

Pierre Pelletier &
Joseph B. Caventou

Powers & Weightman 1822
(Farr and Kunzi, Merck)

François Magendie
(1783-1855)

Conclusion 1: 对于奎宁、士的宁、吗啡的系统定量的研究使药理学研究真正成为一门科学。 These isolation support their use in precision medicine

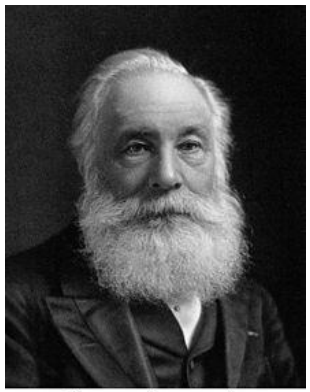
2：奎宁和吗啡的大量生产，标着这真正制药业的诞生-Merck.

3：士的宁、吗啡的分离成功促进了法医毒理学的诞生。

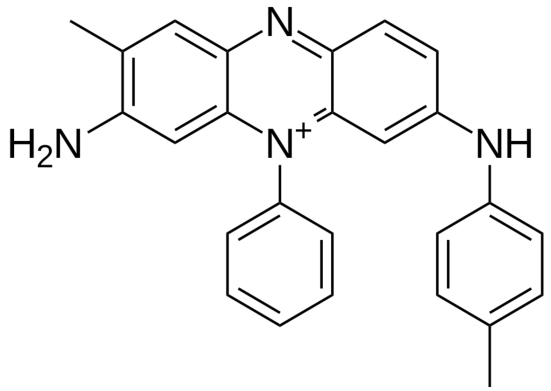
奎宁的合成与苯胺紫的意外发现

因合成奎宁而开启的染料时代–开启了药物科学的春天

A.W. von Hofmann
(1818 – 1892)



William Perkin
(1838–1907)



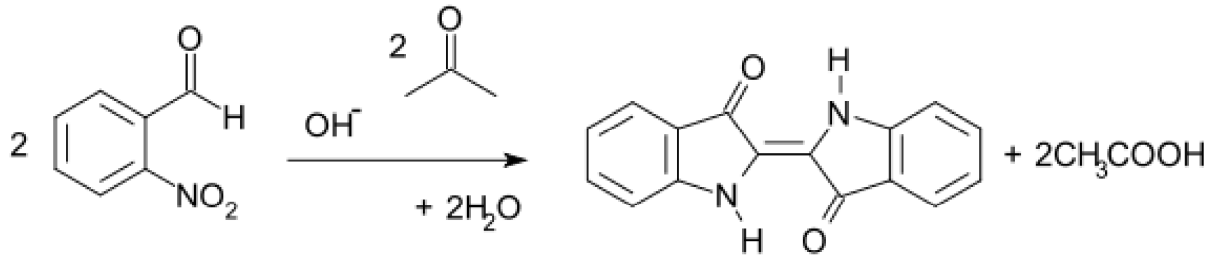
木槿紫accidentally formulated
A teenaged British chemist in1856

背景： 1857年Friedrich A·Kekule提出碳四价理论；1865年提出苯环的结构; 1865年Rudolf Buchheim (1820–1879)建立世界上第一次独立的药理学研究所
1874年van't Hoff 碳价键的正四面体构型

结论1：开启了染料工业化时代

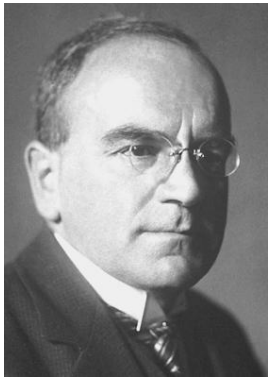
结论2：为Paul Ehrlich寻找“Magic bullet”奠定了基础，为德国制药企业走向世界之巅奠定了基础

经典化学方法研究化学结构的典范



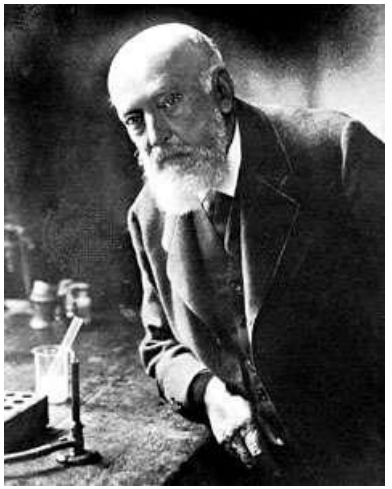
Emil Fischer
1852-1919, 1902 NP

Richard Willstätter
1872-1942, 1915 NP



H. Otto Wieland
1877-1957, 1927 NP

William H. Perkin
1860-1929

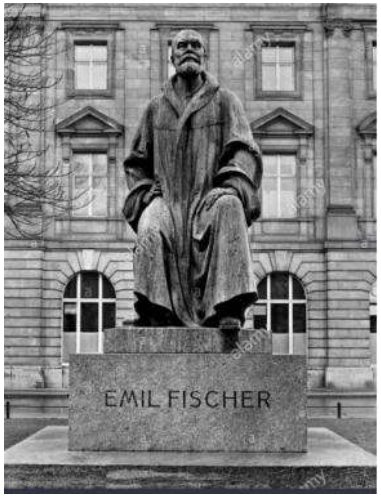


Adolf Von Baeyer
1835-1917
1905 NP

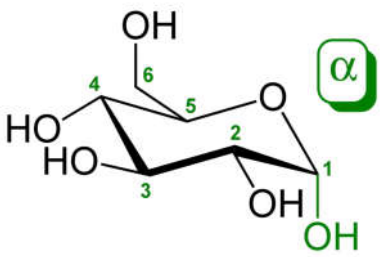
Adolf Von Baeyer synthesized indigo and determined the structure of indigo in 1883—背景： His tutor proposed the structure of Benzene in 1865.

结论： 奠定了用经典化学方法研究药物化学结构的基本方法

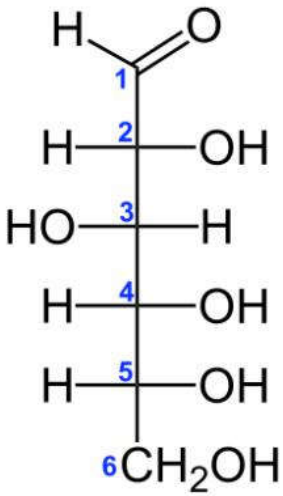
Early Milestone in Biochemistry



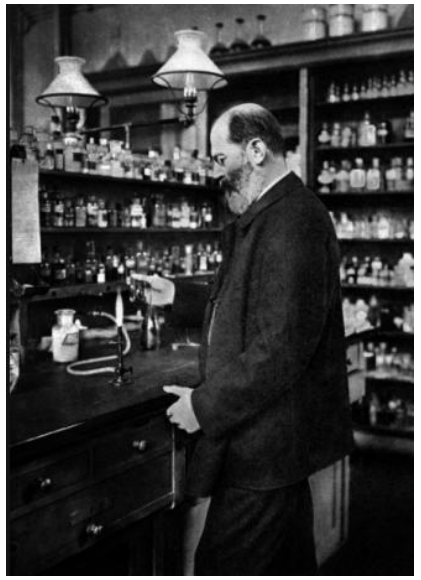
生物化学之父
“糖化学之父”



Glucose
Structure and synthe
in 1890



Fischer projection
D-glucose 1891



Emil Fischer (1852-1919)
One of the world's great chemists

Between 1891 and 1894, Fischer established the stereochemical configuration of all the known sugars and correctly predicted the possible isomers, applying van 't Hoff's theory of asymmetrical carbon atoms.

Conclusion 1： Stereochemical configuration strongly influence the suitability of a molecule to serve as substrate for an enzyme and proposed “Lock and Key” theory.

Conclusion 2： Laid a foundation for the development of biochemistry.

Paul Ehrlich and Chemotherapy

Paul Ehrlich 1854-1915
1908 Nobel Prize

寻找：“Magic bullet” 的人

The Founder of Chemotherapy

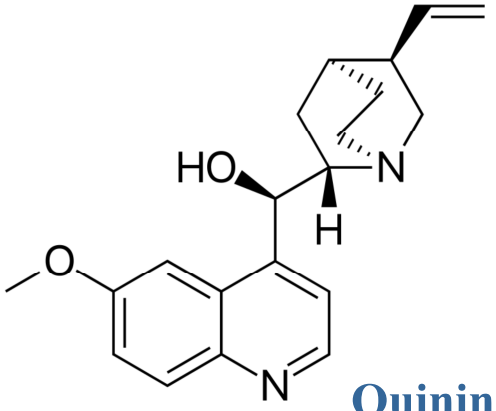
背景： 德国染料工业的发展；细胞理论、组织学、药理学的诞生和发展

Plants were the first source for medications before 20th Century

Conclusion 1. Ehrlich led to the birth of chemotherapy

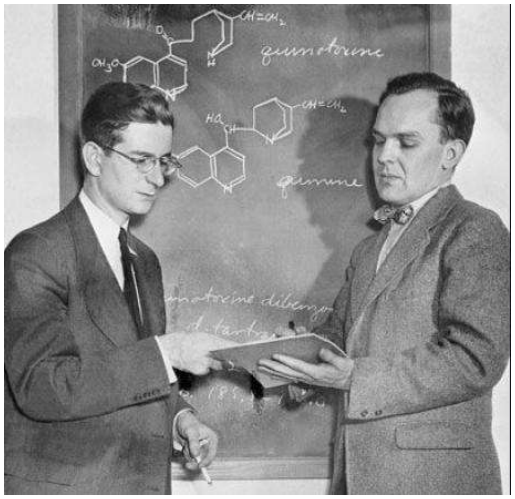
Conclusion 2. Paved the way for finding other drugs such Prontosil and Antibiotics

开启了复杂天然产物全合成



Quinine

"The Woodwardian Era" of organic chemistry



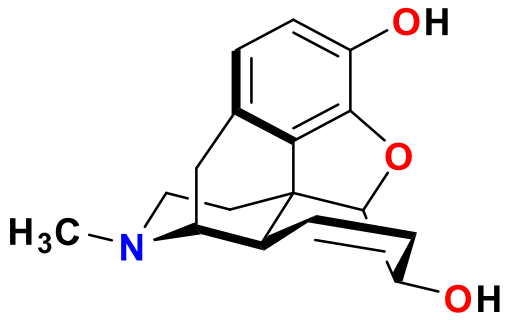
Woodward and Doering, discuss the synthetic scheme for quinine in May 1944

为了解决第二次世界大战造成的奎宁短缺，1944年R. B. Woodward和William E. Doering成功地合成了奎宁毒(D-quinotoxin)，一种被认为可以转化成奎宁的中间体。这个合成被有机化学界认为是一个有机合成史上的里程碑式的成就。结束了对奎宁合成长达100年的探索。

The synthesis of Quinine was viewed as a scientific milestone

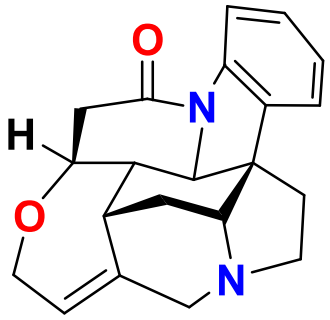
吗啡、士的宁、奎宁等对其他学科的影响

结构研究：一部跨世纪的侦探破案剧



Morphine

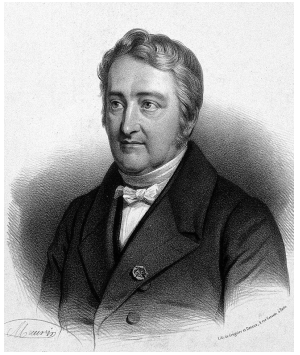
1805-1847-1925-1952



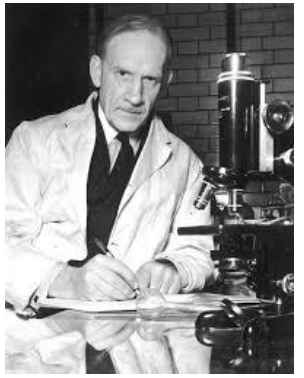
Strychnine

士的宁 1818-1946

Woodward 1954



Marshall D. Gates, Jr.
(1915-2003) A lecturer of 33



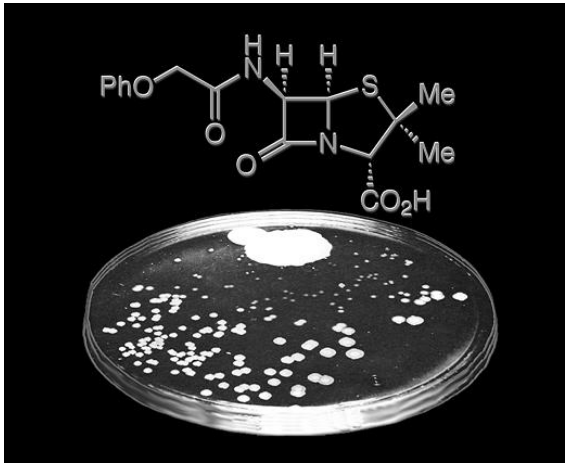
Robert Robinson 1925, 46
Grandmasters of structure determination

结论：医生和药剂师可以准确给药，活性和毒性都增加了

天然药物化学对有机化学、分析化学、药理学、 生理学、法医毒理学等学科的发展都有重大影响

Not Just A Serendipity Finding

A Milestone in the Development of Antibiotics



A famous petri dish
Discovered in 1928 but 1943 in clinic.

Team for structure

Alexander Fleming
(1881-1955)

在战火纷飞的年代,组织一支互补的专业团队，将一个已被世人遗忘了10多年的论文从故纸堆里找出来，克服二战中的重重困难，把青霉素成功推向应用，让青霉素焕发出应有的光芒。青霉素、安定、阿司匹林-并称世界医学史上三大经典药物。5位诺奖得主参与结构研究。

结论：制药企业开始建立研发机构，促进美国制药企业的升级改造；开始抗生素的黄金时代，开启了药企主导药物研发；药物研发的典范。

明德博學
行方智圓

谢谢大家

药学院403室 QQ 46897262 Tel 86261270

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