
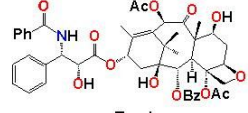


“War on Cancer”



Camptothecin
Camptotheca acuminata



Taxol
Taxus brevifolia



Target Identification	Inhibitors Identification	Lead Identification	Medicinal Chemistry	Cellular & Molecular Pharmacology	Preclinical Development
Target Validation	Toxicity Evaluation	ADME Development	Library Development	In Vivo Target Activity	Preclinical Toxicology

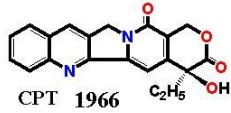
➔

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

喜树碱 Camptothecin



CPT 1966 $C_{25}H_{38}O_6$

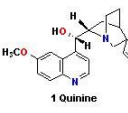
1958 Dr. Wall & Wani

10-Hydroxycamptothecin is used in China to treat cancers of the liver and stomach and also leukaemias.


- [来源] 珙桐科植物喜树 *Camptotheca acuminata* 全株; 茜草科植物蛇根草 *Ophiorrhiza mungos* 叶。
- [活性] 抗肿瘤。对DNA拓扑异构酶I有明显抑制作用。

Craig J. et al. *Bioorg. Med. Chem.* 2004,12: 1585-1604.

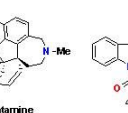
Natural Products and Medicines



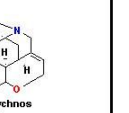
1 Quinine



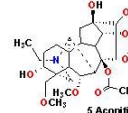
2 Morphine



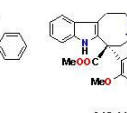
3 Galantamine



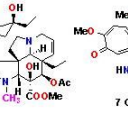
4 Strychnos




5 Aconitine



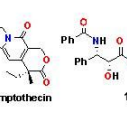
6 Vinblastine



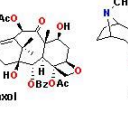
7 Colchicine



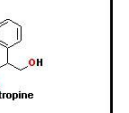
8 Camphor



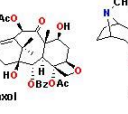
9 Menthol



10 Camptothecin




11 Taxol



12 Atropine

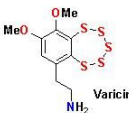
Marine: Unique Environment and Peculiar Organism

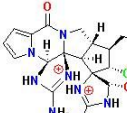


海洋中有: 1) 丰富多样的生物物种, 其品种是陆地上的两倍以上, 无论大小、软硬、抑或速度快慢, 都能生存下来, 这说明它们有天然自卫、抵抗疾病的能力。特别是那些身上充满生物活性分子、利用化学方式保护自己的海洋物种, 很可能蕴含丰富的药物资源。2) 特殊的生态环境。

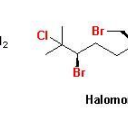
Marine: A Rich Treasure Chest of New Drug ?



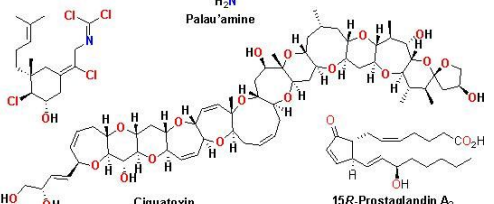
Varicin



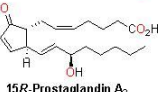
Palau'amine



Halomon





Ciguatoxin




15R-Prostaglandin A₂

Drugs From The Sea ?





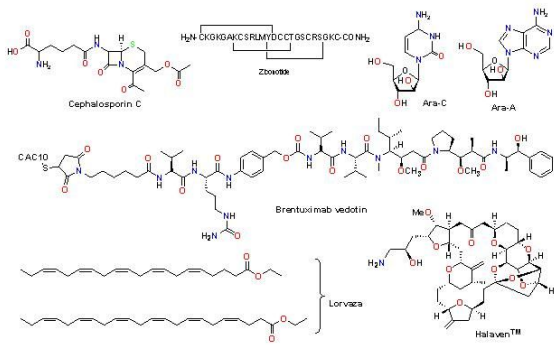
ET-743
曲贝替定



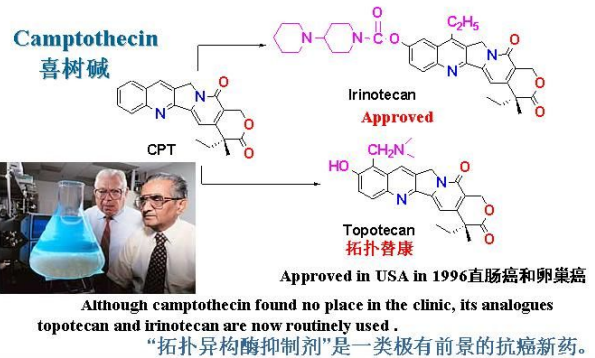
ET-743 对晚期软组织癌症如直肠癌, 乳腺癌, 肺癌, 黑色素瘤等有显著的疗效。来源于被囊动物红树海鞘 *Ecteinascidia turbinata*。

2007年9月欧盟已批准该药(商品名 Yondelis[®])用于晚期软组织肿瘤的治疗, 成为第一个现代海洋药物。

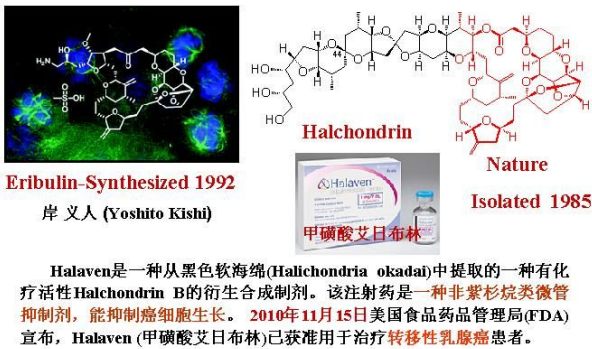
Will Next Anti-cancer Come From Ocean?



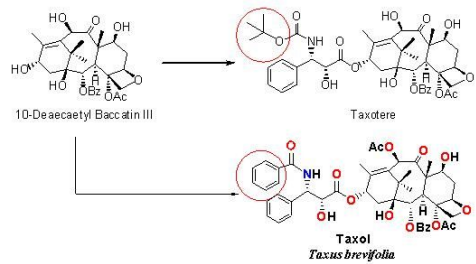
先导化合物 (Lead Compound)



Better Than Nature



Better Than Nature



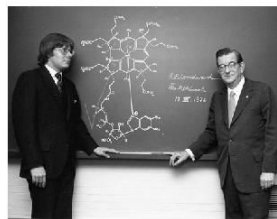
半合成的多西紫杉醇又称紫杉特尔(Taxotere®)溶解性比紫杉醇更好，活性是紫杉醇2.7倍。

天然药物化学的应用

- ◆ 探索植物(中药)、动物、海洋生物等防病治病的物质基础
- ◆ 发现新药、寻找先导化合物
- ◆ 促进其他学科的发展—有机化学，分析化学，生命科学

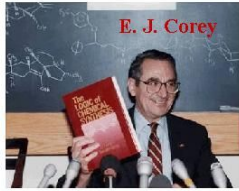
天然产物化学促进有机化学的发展

Natural product synthesis has indeed been the impetus for many fundamental discoveries (Vitamin B₁₂—Pericyclic Reaction and Woodward-Hoffman Rule)



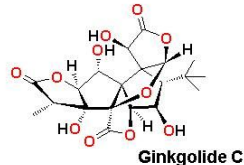
Woodward and Mark Wuonola on March 17, 1976, the day that the synthesis of Vitamin B₁₂ was completed. Robert Robinson 1965 and Hoffmann 1981 NP.

天然产物化学促进有机化学的发展



Retro-synthetic Analysis 1990

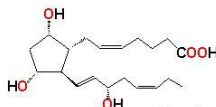
OCSS: Organic Chemical Synthesis Simulation



Ginkgolide C



Longifolene

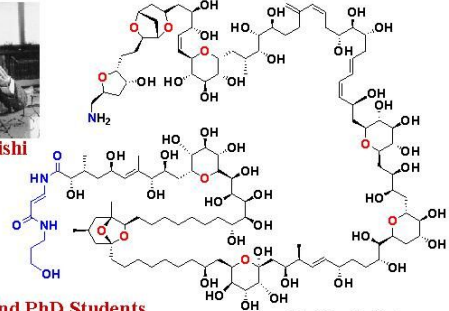


Prostaglandins

天然产物化学促进有机化学的发展



Yoshito Kishi



21 P-PhD and PhD Students spend more than 8 years in 1992

岩沙海葵毒素 PTX

天然产物化学促进分析化学的发展



Richard R. Ernst (瑞士)因发明了傅立叶变换核磁共振分光法和二维核磁共振技术在1991年获得诺贝尔化学奖。



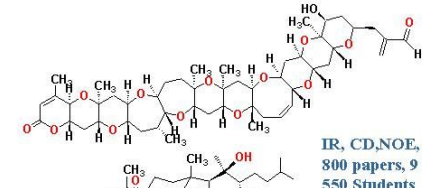
Dorothy Crowfoot Hodgkin 因用X射线衍射方法研究青霉素和维生素B₁₂等的分子结构成功,英国科学家霍奇金在1964年获得诺贝尔化学奖。

天然产物化学诺贝尔奖候选人

A Wandering Natural Products Chemist-Nakanishi Koji



达纳康(Tanakan®)



IR, CD, NOE, NMR
800 papers, 9 books
550 Students

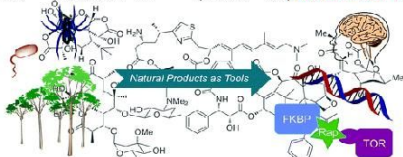


Dr. Elias Corey, University of Texas at Austin, © Science Channel



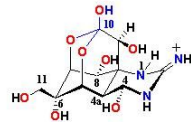
天然产物化学促进生命科学的发展

天然产物作为化学和生物学之间一个天然的通道,是大自然经过漫长的筛选和进化选择出来的。生命科学的发展急需应用新的小分子作为分子探针去帮助研究已知的生物反应机理,去发现尚未被阐明的生物作用机理,去验证全新的生物药物靶点,和去解决重大的医学难题。天然产物作为化学小分子探针做出了其他生物技术方法无法企及的特殊贡献,并此催生了一门新的学科——(天然产物)化学生物学。

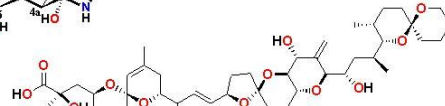


Erin E. Carlson. Natural Products as Chemical Probes. ACS Chem. Biol. 2010, 5, 639-653.

Natural Products as Modulators of Bio-molecular Function

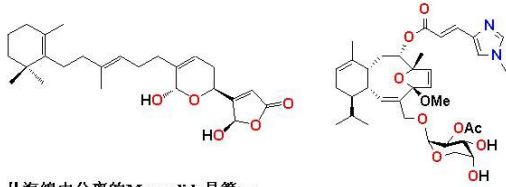


Tetrodotoxin has been used extensively as a tool in the study of sodium channel pharmacology.



大田软海绵酸(Okadaic Acid)是一种肿瘤促进剂,能抑制由钙激活的磷脂依赖的蛋白激酶,是一种特殊的蛋白质磷酸酶1、2A和2B的抑制剂,作为研究细胞调控的工具药。

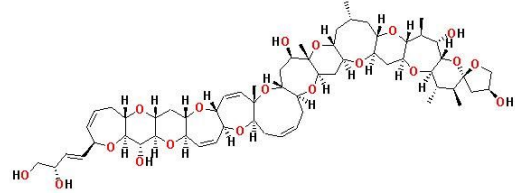
Natural Products as Modulators of Bio-molecular Function



从海绵中分离的Manoalide是第一个具有选择性作用于磷脂酶A2 (PLA2), 现已成为研究阻断PLA2的常规工具药。

Eleutherobin 从软珊瑚中分离的二萜苷, 具有紫杉烷一样的抗癌机制, 对乳腺、肾、卵巢及肺癌细胞有极高的选择性, 是未来几年有望发展为抗癌剂的候选化合物。

Natural Products as Pharmacologic Tools to Explore Bio-molecular Function



西加毒素(Ciguatoxin, CTX)是电压依赖性Na⁺通道激动剂, 可作为研究兴奋细胞膜结构与功能以及局麻药作用机理的分子探针。

CTX 属于新型的钠通道激动剂, 是引起人类中毒分布最广的一种毒素2-6万人/年

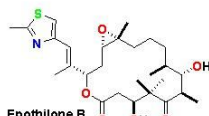
Natural Products as Pharmacologic Tools to Study Signaling Pathway



Brefeldin A is a fungal metabolite used as a biological research tool for studying protein transport.

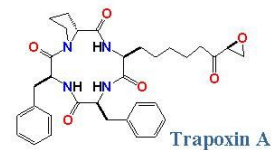
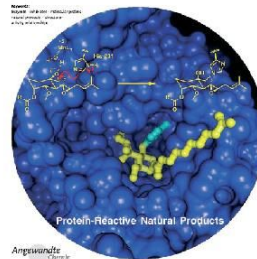


Trapoxin A是组蛋白去乙酰化酶(histone deacetylases)抑制剂



Epothilone B has similar modes of action to Taxol and is derived from the fermentation of *Sorangium cellulosum*.

Protein-Reactive Natural Product



Trapoxin cause cell cycle arrest in mammalian cells and inhibit histone deacetylation.

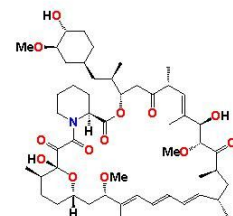
Drahl, C., Cravatt, B. F., and Sorensen, E. J., *Angew. Chem., Int. Ed. Engl.* 2005, 44, 5788.

Natural Products as Chemical Probes



Rapamycin 雷帕霉素是1975年加拿大 Ayerst 实验室 Vezina 等从南太平洋 Easter 岛土壤样品中分离的吸水链霉菌 (*Streptomyces hygroscopicus*) 所产生的一种含氮大环内酯类免疫抑制药。1989年 Morris 等首次将其用于抗器官移植排斥反应, 发现对外周血单核细胞的有效抗增殖作用比环孢素 (C17A) 强 50-500 倍, 肾毒性比环孢素低。1999 年应用于临床。

Natural Products as Chemical Probes



Rapamycin
雷帕霉素

雷帕霉素靶点
mTOR 信号途径

Rapamycin and its derivatives have played important roles in the clarification of several cellular processes including cell growth, proliferation, and survival as well as protein synthesis and transcription.

ACS Chem Biol. 2010; 5(7): 639-653

Bottcher T, Pitscheider M, Sieber SA. Natural products and their biological targets: Proteomic and metabolomic labeling strategies, *Angew. Chem., Int. Ed.* 2010, 49, 2680-99.