

Natural Products. A History of Success and Continuing Promise for Drug Discovery and Development



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Developmental Therapeutics
Program

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EARLY DOCUMENTATION OF USE OF MEDICINAL PLANTS

<http://www.nlm.nih.gov/hmd/collections/archives/index.html>

- Mesopotamian ~2,600 B. C. E.
- Egyptian ~ 1,800 B. C. E.
- Chinese – ~1,100 B. C. E. and continuing
- Indian ~ 1,000 B. C. E. and continuing
- Greek ~ 500 B. C. E.

Greco-Roman expertise preserved and coordinated with other traditions by Islamic cultures during the Dark Ages ~ 400-1,100 CE

**Avicenna. Persian pharmacist,
physician, poet, philosopher
author: canon medicinae –
“final codification of Greco-Roman
medicine”**



Great Moments in Pharmacy Collection APhA

Traditional Medicine and Drug Discovery

- 80% of the world population resides in developing countries
- 80% of people in developing countries utilize plants to meet their primary health care needs
- Global pop. ca. 7 billion → ca. 4.5 billion people utilize plants to meet their primary health care needs



Norman Farnsworth

Farnsworth NR, et al. Medicinal Plants in Therapy. *Bull. W.H.O.* 63:965-981 (1985)

Fabricant and Farnsworth, *Environ. Health Perspect.* 109, 69-75 (2001)

Cordell and Clovard, *J. Nat. Prod.*, 75, 514-525 (2012)

1800s. Discovery of some active principles of major herbal preparations

Newman and Cragg. *Natural Product Chemistry for Drug Discovery*, eds. Buss and Butler, M. S., Royal Soc. Chem., Cambridge, 2010, pp. 3-27

European chemists (apothecaries) revolutionized drug discovery and development.

1817. Sertürner reports isolation of **morphine** from *Papaver somniferum*.

Commercialized by E. Merck in Darmstadt in 1827

1820. Pelletier & Caventou – **quinine** from *Cinchona* species

1820. Pelletier & Caventou - **colchicine** from *Colchicum autumnale* and codeine (*P. somniferum*)

1832. Robiquet – **codeine** from *Papaver somniferum*

1839. Pirai - **salicylaldehyde** from *Salix* species, converted to **salicylic acid**. **Acetyl salicylic acid** synthesized by Gerhard in 1853. Developed at Bayer as the drug, **aspirin**, in 1899.

1848. G. F. Merck –**papaverine** from *P. somniferum*.

1875. Schmiedeberg – **digitoxin** from *Digitalis purpurea*

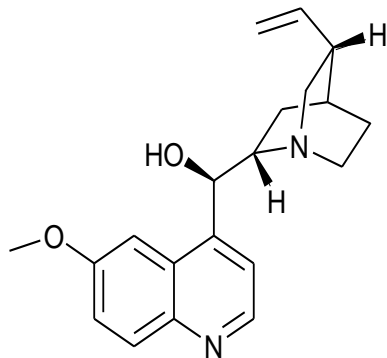
ANTIMALARIAL DRUGS – THE ROLE OF TRADITIONAL MEDICINE

Marella et al., *Malaria. Hitches and Hopes*, *Mini Rev. Med. Chem.*, 2014, 453-470

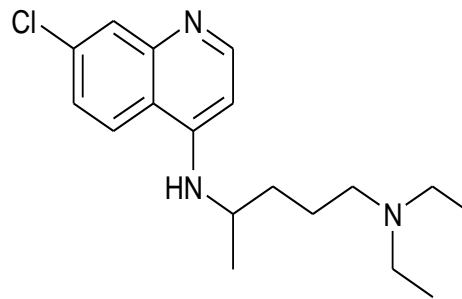
Quinine from *Cinchona spp.* used in the Amazon region for centuries for treatment of fevers



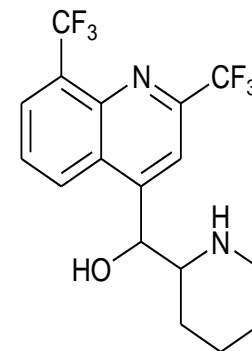
249. *Quinine* (from *Cinchona*) — *Cinchona succubida* Pers.



Quinine

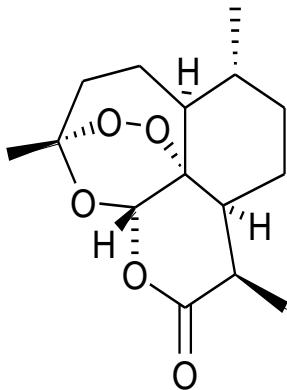


Chloroquin

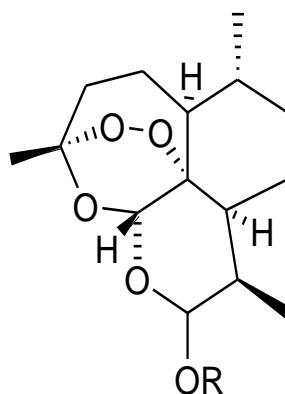


Mefloquine

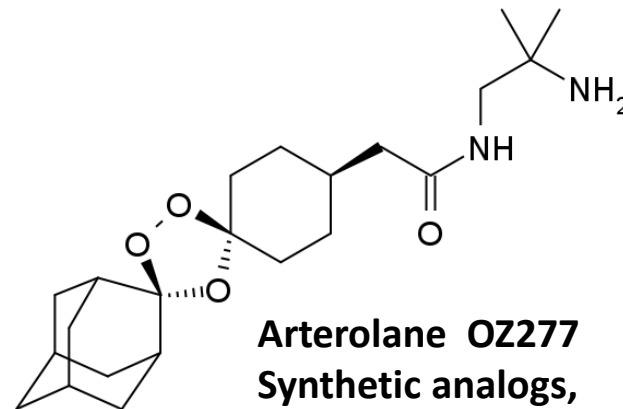
Artemisinin from *Artemisia annua* used in TCM for centuries for treatment of fever - developed for the treatment of drug resistant malaria.



Artemisinin



Artemether R = CH₃
Arteether R = CH₂CH₃

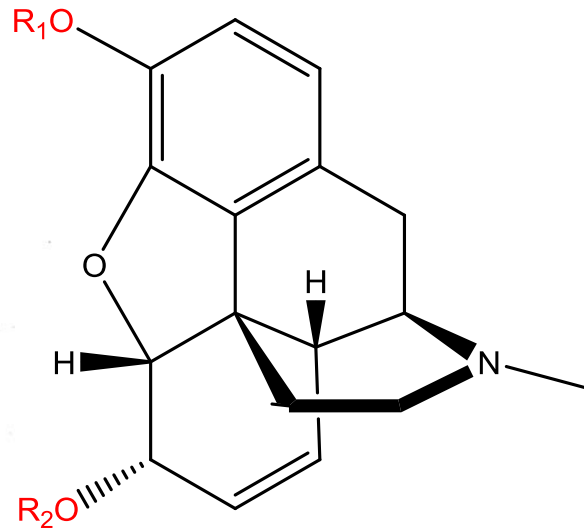


Arterolane OZ277
Synthetic analogs,
Vennerstrom et al., *J. Med. Chem.*, 2013, 56,
2547–2555

MORPHINE – AN INDISPENSABLE PAINKILLER

Isolated from *Papaver somniferum*

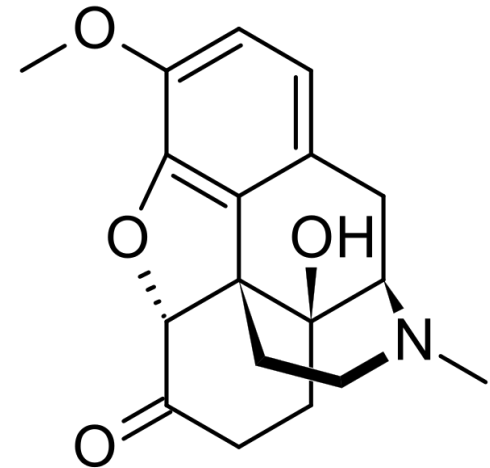
Katz and Benoit, Opioids for neuropathic pain. Curr. Pain Headache Rep., 2005, 9(3):153-60.



Morphine: R₁ = R₂ = H

Codeine: R₁ = CH₃ ; R₂ = H

Heroin: R₁ = R₂ = COCH₃



Oxycodone

In clinical use since 1917



Fleurs et capsules du pavot (*Papaver somniferum*, Papaveraceae). Le latex blanc, c'est l'opium.

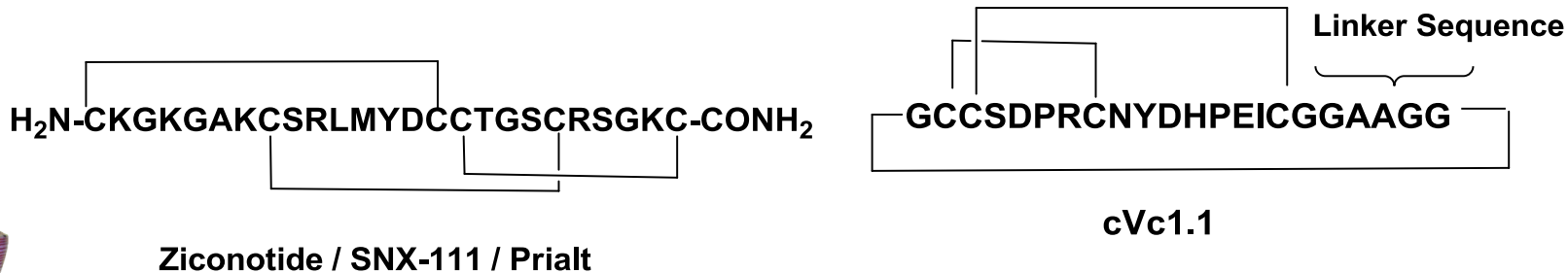
COMBINATORIAL PEPTIDE LIBRARIES IN DRUG DESIGN. LESSONS FROM VENOMOUS CONE SNAILS

Olivera et al., J. Biol. Chem., 2003, 278, 2177-2183; Curr. Pharm. Des. 2008,14,2462-79; Lewis et al., Pharmacol. Rev. 2012, 64, 259-98



Balmadero Olivera
Univ. Utah

Cone snails pioneered a combinatorial library strategy to evolve highly bioactive venom peptides targeting cell surface receptors or ion channels



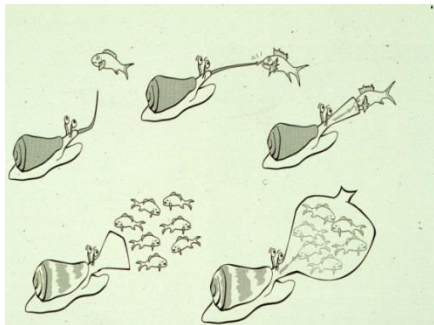
Ziconotide isolated from *Conus majus* for treatment of intractable neuropathic pain

- Potent activity against voltage-gated Ca^{2+} channels
- Approved by FDA in Dec. 2004. Marketed as Prialt®
- Application limited due to difficult delivery via intrathecal infusion from reservoir in peritoneum.

Synthesis of orally bioavailable cyclic analogs (e.g, cVc1.1)

Craik et al., Angew. Chem. Int. Ed., 2010, 49, 6545-48; Fut. Med. Chem., 2012, 4, 1243-55.

120 times more potent than gabapentin in animal models in the treatment of neuropathic pain.

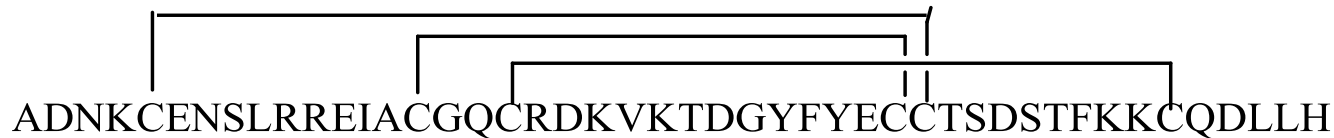


VENOMS AS SOURCES OF POTENTIAL ANALGESICS

King, Expert Opin. Biol. Ther., 2011, 11, 1469-1484

Pain: Targets - e Na_v1.7, 1.8 and 1.9 voltage-gated sodium ion channel subtypes found in peripheral nervous system. Na_v1.7 is the most 'exciting' analgesic target. 6 other subtypes found in brain, heart, and muscle tissue.

Halford, C&EN, 2014 (Mar. 24), 92 (12), 10-14



μSLPTX. From venom of the Chinese red-headed centipede *Scolopendra subspinipes mutilans*: potent, selective blocker of Na_v1.7 channel.

Yang, King et al., Proc. Nat. Acad. Sci., 2013, 110, 17534-17539

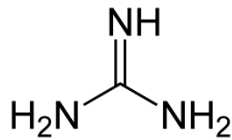


Protoxin-1. From venom of the Peruvian green-velvet tarantula, *Thrixopelma pruriens*. Spider-venom peptides are generally potent, but not selective, sodium channel blockers Klint, King et al., Toxicon, 2012, 60, 478-491.

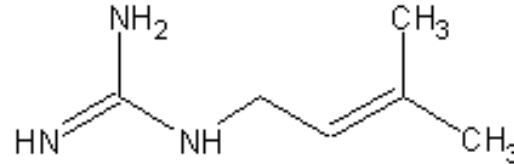


TREATMENT OF TYPE 2 DIABETES – NATURAL INSPIRATION

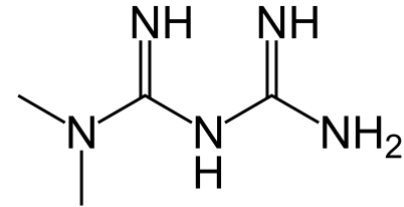
Krentz and Bailey, Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs*. 2005;65(3):385-411



Guanidine



Galegin



Metformin
Synthesis, 1922

Galega officinalis

Herbal use to treat polyuria (excessive urination) associated with Type 2 diabetes. Metformin decreases hyperglycemia primarily by suppressing liver glucose production. Also being developed for treatment of cancer. Leone et al., *Cancer Treat. Res.* 2014,159,355-76.



H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂

Exenatide (Byetta; Bydureon). Synthetic version of exendin-4 from saliva of the Gila Monster, *Heloderma suspectum*. Triplitt & Chiquette, *J. Am Pharm Assoc*, 2006, 46, 44-52; Cvetković & Plosker, *Drugs*, 2007,67, 935-54.

Mimics natural incretin hormones that stimulate the release of insulin in response to a meal. FDA approved use in 2005 but is investigating possible increased risk of pancreatitis and pre-cancerous cellular changes/pancreatic duct metaplasia

<http://www.fda.gov/drugs/drugsafety/ucm343187.htm>

THE MICROBIAL WORLD OF BACTERIA AND FUNGI

SOURCE OF CHEMICAL DIVERSITY

AND

WONDER DRUGS



Alexander Fleming – serendipitous discovery of penicillin in 1928



Lentinus edodes (Berk.) Sing.



7. *Condyceps militaris*

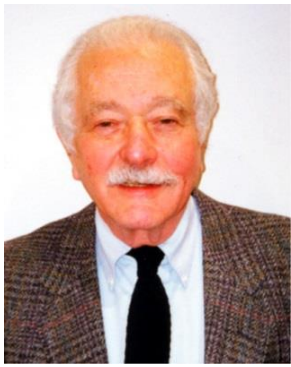
Jianzhe, Ying, et al. *Icons of Medicinal Fungi from China*, 1987:16

MICROBIAL-DERIVED DRUGS

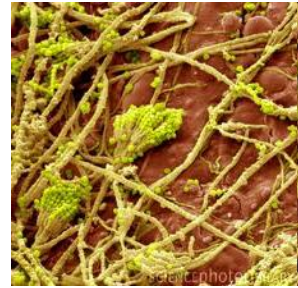
**Demain and Sanchez, Microbial drug discovery:
80 years of progress.**

J. Antibiot (Tokyo), 2009, 62(1):5-16.

**Singh and Barrett, Empirical antibacterial drug
discovery--foundation in natural products.
Biochem. Pharmacol., 2006, 71,1006-15**



Arnold Demain



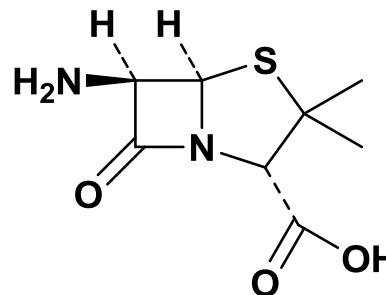
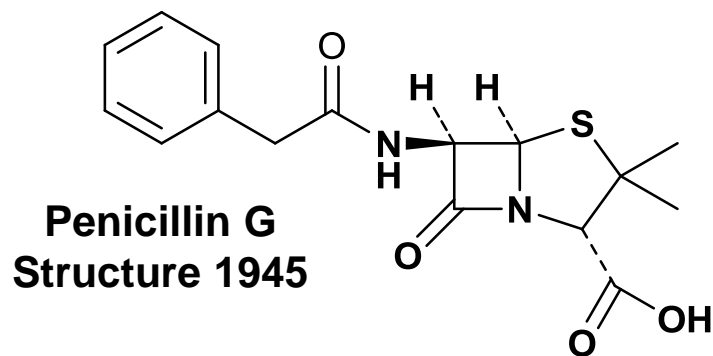
- **Penicillins (*Penicillium spp.*); cephalosporins (*Cephalosporium acremonium*); glycopeptides, tetracyclines, polyketides (*Streptomyces spp.*)**
- **Immunosuppressive agents: Cyclosporin, rapamycins (*Streptomyces spp.*)**
- **Cholesterol-lowering agents: Mevastatin, lovastatin, etc. (*Penicillium spp.*)**
- **Anticancer drugs: Anthracyclines (e.g., doxorubicin), bleomycins, mitomycins, staurosporins (*Streptomyces spp.*); epothilones (*Myxobacteria*)**

Demain, Antibiotics: natural products essential to human health. Med. Res. Rev. 2009, 29(6), 821-42.

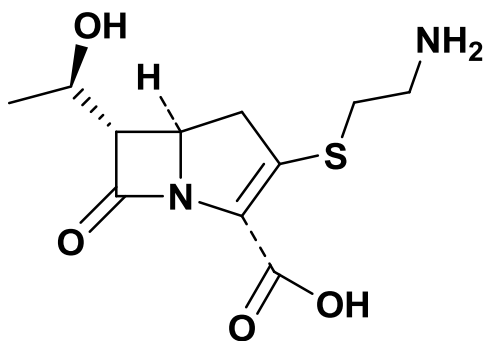
Newman & Cragg, Natural Products of Therapeutic Importance. In Comprehensive Natural Products II Chemistry and Biology; Mander & Lui, Eds.; Elsevier: Oxford, 2010; volume 2, pp.623–650.

Penicillins (*Penicillium spp.*).

Kardos and Demain, Penicillin: the medicine with the greatest impact on therapeutic outcomes. Appl. Microbiol. Biotechnol., 2011, Nov;92(4), 677-87

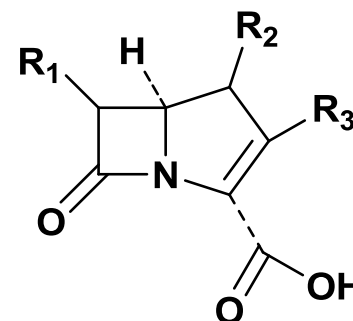


6-Aminopenicillanic acid. Basis for synthesis of multiple penicillin analogs



**Thienamycin
S. Cattleya 1976**

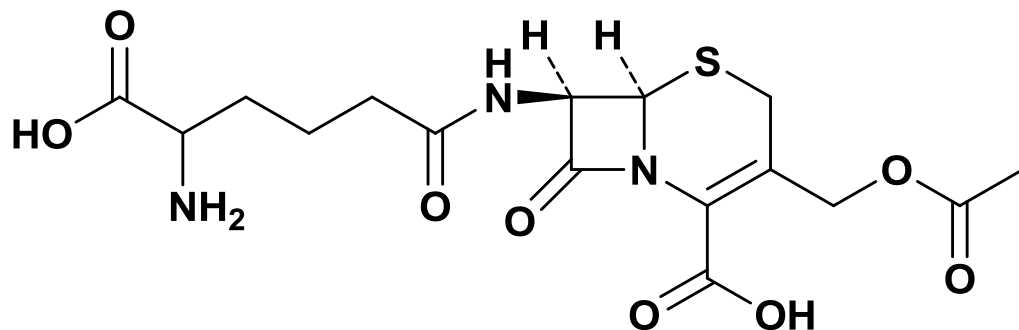
Thienamycin is resistant to β -lactamases. Its discovery formed the basis for the synthesis of many carbapenems which have been a last resort in the treatment of many drug resistant bacterial infections.



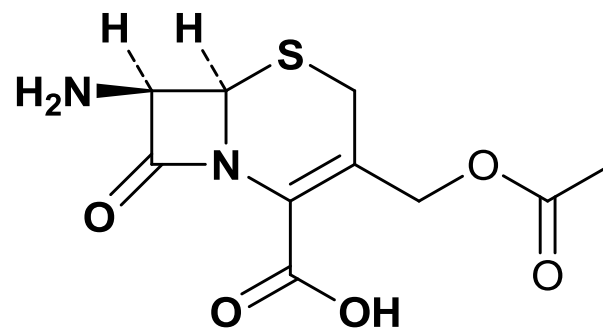
Carbapenems

Cephalosporins (*Cephalosporium acremonium*)

Long and Williams, Cephalosporins currently in early clinical trials for the treatment of bacterial infections. *Expert Opin. Investig. Drugs*. 2014, 23
Posted online on June 23, 2014. (doi:10.1517/13543784.2014.930127)



Cephalosporin C
Reported 1948
Structure 1961

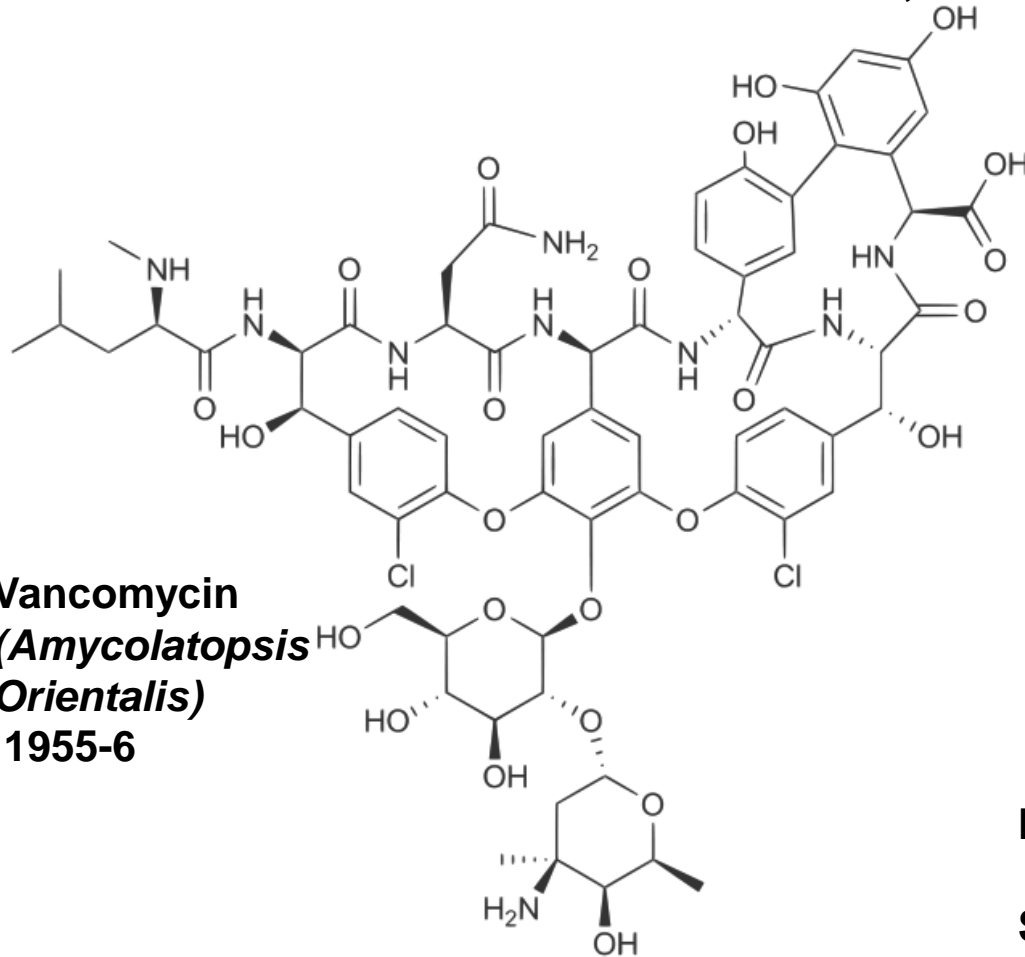


7-Aminocephalosporanic acid

Estimated that well over 20,000 penicillin and cephalosporin-based molecules have been produced by semi- and total syntheses based on 6-aminopenicillanic acid and 7-amino-cephalosporanic acid.

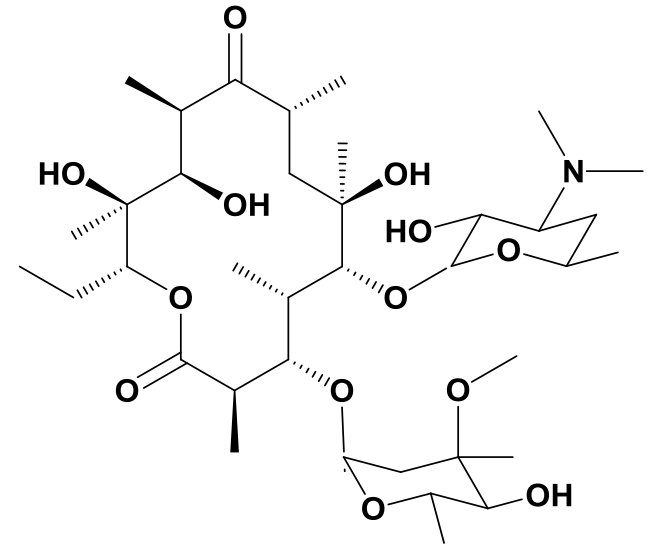
Glycopeptides and Polyketides

Kahne et al., Glycopeptide and lipoglycopeptide antibiotics. Chem Rev., 2005,105(2), 425-48; Katz L, Ashley GW. Translation and protein synthesis: macrolides. Chem Rev., 2005, 105(2), 499-528



Vancomycin
(Amycolatopsis Orientalis)
1955-6

Semi-synthetic derivatives: Oritavancin, Telavancin/FDA approved 2009, Dalbavancin/ approved by FDA May 23, 2014, both for treatment of skin infections

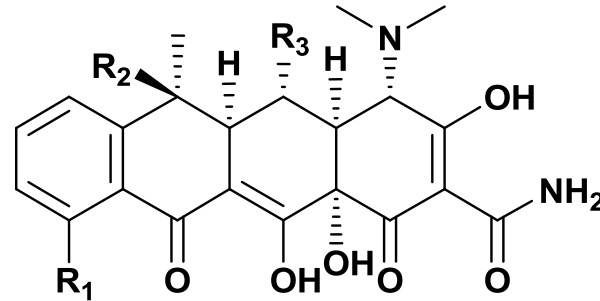


Erythromycin (*Streptomyces erythreus*)
1952

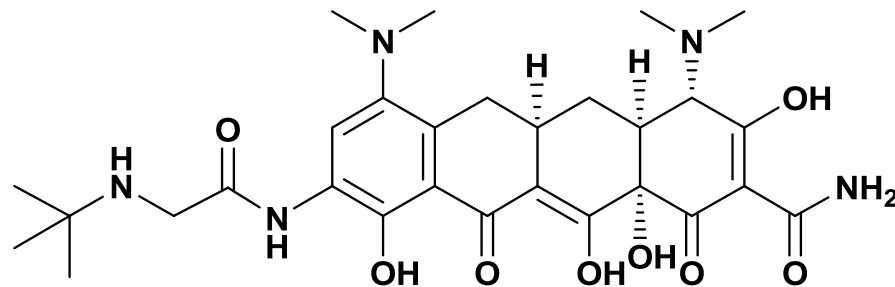
**Semi-synthetic derivatives:
Telithromycin (Ketek). FDA approved 2004; safety warnings 2007
Cethromycin (Restanza)
EDP-420.**

Tetracyclines

Petković et al., Genetics of *Streptomyces rimosus*, the oxytetracycline producer.
Microbiol. Mol. Biol. Rev. 2006 Sep;70(3):704-28;.



Tetracycline (*Streptomyces viridifaciens*) (R₁= R₂= OH; R₃= H) 1955
Aureomycin (*S. aureofaciens*) (R₁= Cl; R₂= R₃= H) 1945
Oxycycline (*S. rimosus*) (R₁= R₂= R₃= OH) 1950
Doxycycline (semisynthetic) (R₁= OH; R₂= H; R₃= OH) 1962

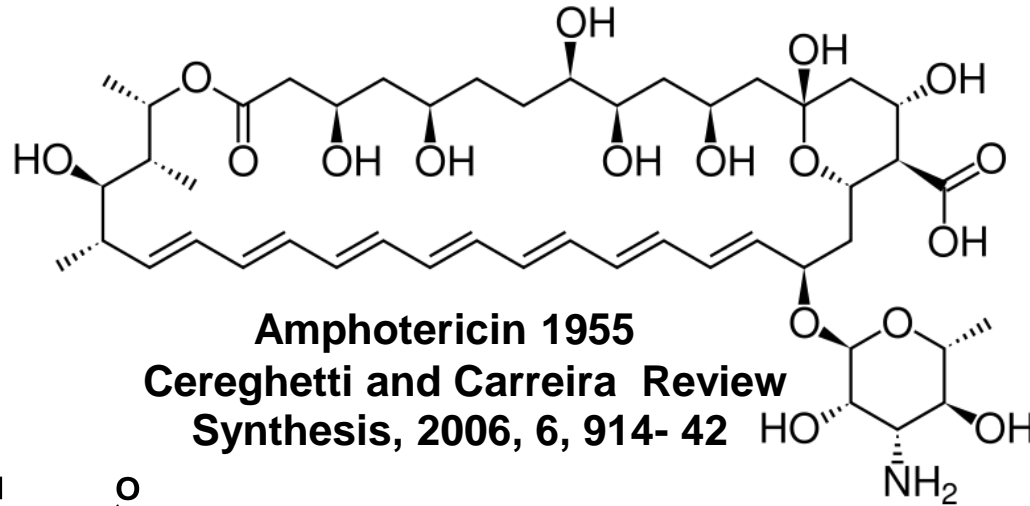


Tigecycline (Tygacil)

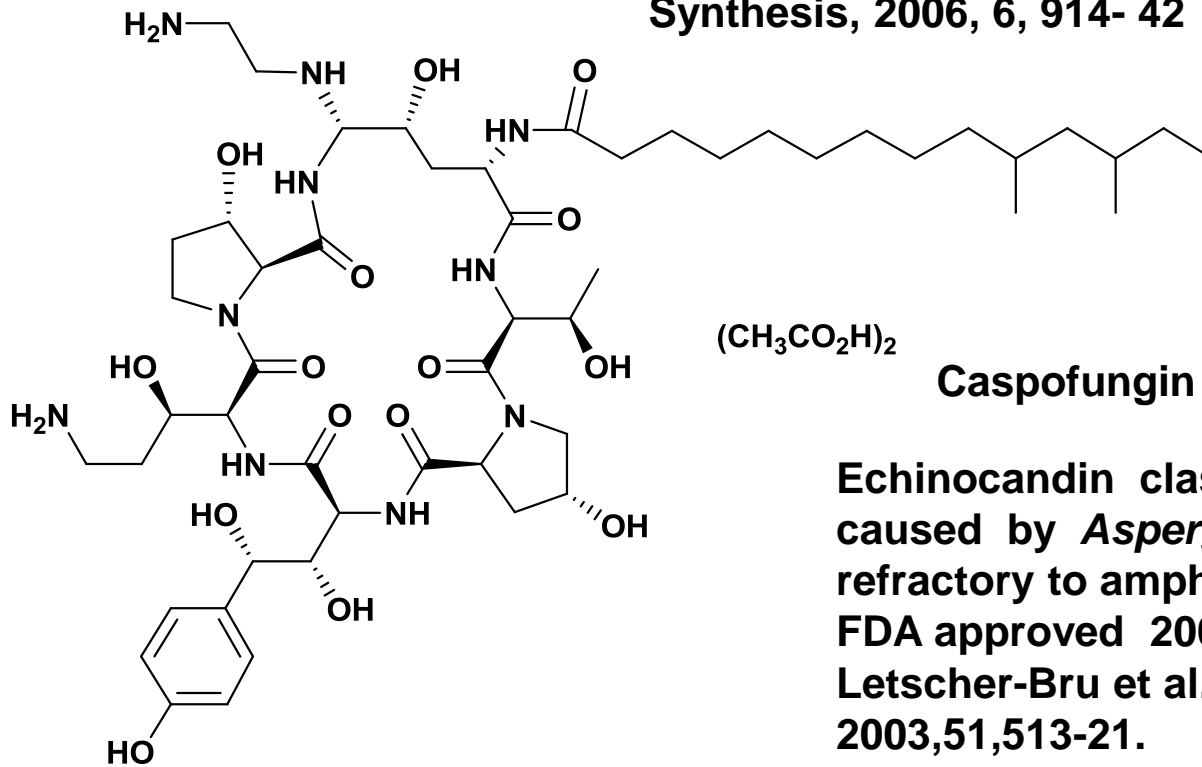
FDA approved 2005. Active against drug resistant *Staphylococcus*
and *Enterococcus* spp. and *Streptococcus pneumoniae*.
Wenzel et al., Nat. Rev. Drug Discov. 2005, 4, 809-10.

Antifungal Antibiotics

Roemer et al., Confronting the challenges of natural product-based antifungal discovery. Chem. Biol. 2011 18 :148-64



Amphotericin 1955
Cereghetti and Carreira Review
Synthesis, 2006, 6, 914- 42



$(\text{CH}_3\text{CO}_2\text{H})_2$

Caspofungin (Cancidas)

Echinocandin class. Active against infections caused by *Aspergillus* and *Candida* species refractory to amphotericin.

FDA approved 2001

Letscher-Bru et al., J. Antimicrob. Chemother., 2003,51,513-21.

A Bacterial Battle. Bacteria are Outsmarting Us!

Jarvis, C&EN, 2014 (June 16), 92(24), 9-14

Antibiotic Resistance Factors

- Inactivation of antibiotics by enzymatic reactions (e.g., inactivation of β -lactams by β -lactamase)
- Efflux mechanisms by which antibiotics are transported out of cells by pumps (e.g., tetracyclines subject to tet M efflux pumps)
- Target mutation to decrease binding efficiency of antibiotics (e.g., modification of D-Ala-D-Ala to D-Ala-D-Lac making vancomycin less effective)
- Overproduction of target (e.g., DHFR)
- Bypass of the metabolic pathway to remove the essentiality of the target (e.g., peptide deformylase in *Streptococcus pneumoniae*)
- Decreased uptake of antibiotics (e.g., *Pseudomonas aeruginosa* loss of its D2 porin)

Antibiotic Resistance: Walsh & Wright, Eds., Chem. Rev., 2005, 105,(2), 391-774

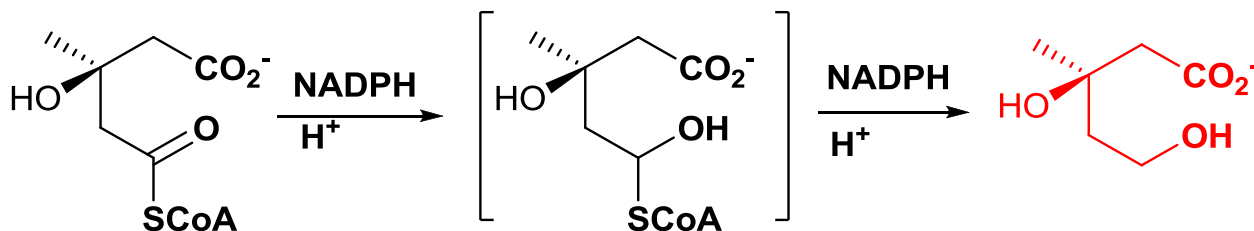
16 papers covering Aminoglycosides, Antifolates, Antitumor antibiotics, Glycopeptides and Lipoglycopeptides, β -Lactams, Lantibiotics, Macrolides and polyketides, Streptogramins and Oxazolidinones, Quinolones and pyridones, Rifamycins, Thiopeptides.

Davies and Davies, Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010 Sep;74(3):417-33.

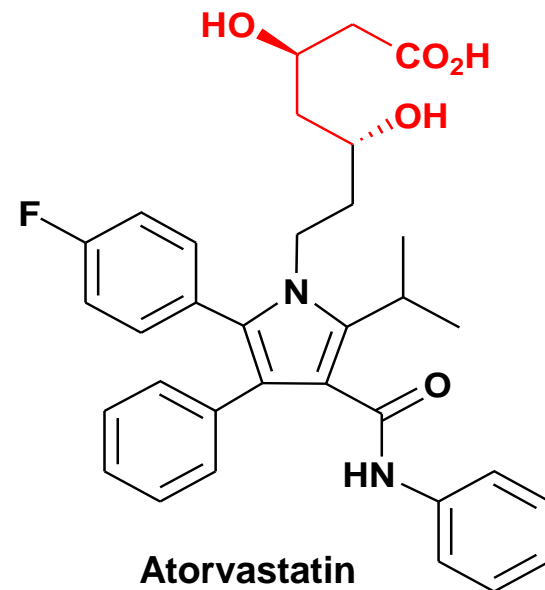
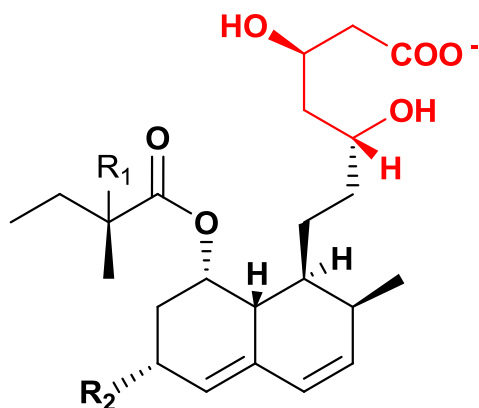
CHOLESTEROL LOWERING DRUGS

The Birth of the Statins – A Valuable Gift from Nature

Lasker-Debakey Clin. Med. Research Award: Endo, Nat. Med., 2008, 14, 1050-1052;
Steinberg, J. Lipid Res., 2006, 47, 1339-1351



Mevalonate



Atorvastatin
(Lipitor)
FDA approval 1996



Akiro Endo
Biopharm Res.
Labs., Japan

Compactin: $R_1 = R_2 = H$; from *Penicillium centrinum*,
Endo et al., *J. Antibiot*, 1976, 29, 1346-1348

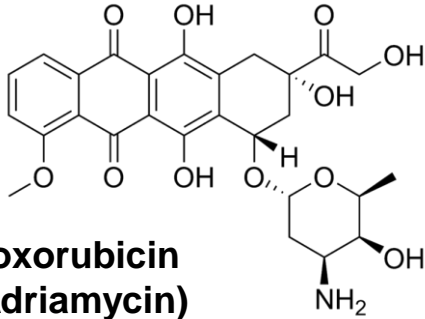
Lovastatin: $R_1 = H$, $R_2 = CH_3$; from *Aspergillus terreus*, FDA approval
1987; Alberts et al., *Proc. Natl. Acad. Sci.*, 1980, 77, 3957-3961

Simvastatin: $R_1 = R_2 = CH_3$; FDA approval 1991

Pravastatin: $R_1 = H$, $R_2 = OH$; FDA approval ; FDA approval 1991

ANTITUMOR ANTIBIOTICS

Anticancer Agents from Natural Products. Cragg, Kingston, and Newman, (Eds.),
2nd Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012.



**Doxorubicin
(Adriamycin)**

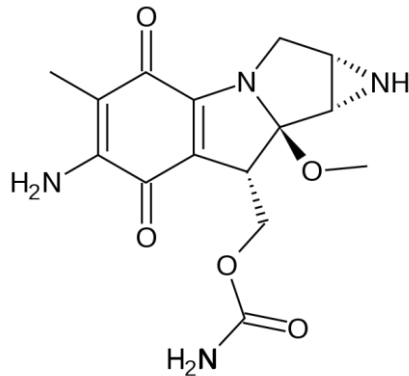
S. peuceetius 1969

FDA approval 1974

Semisynthetic derivs:

Epirubicin. FDA approval, 1999

Idarubicin (Idamycin). FDA approval, 1990



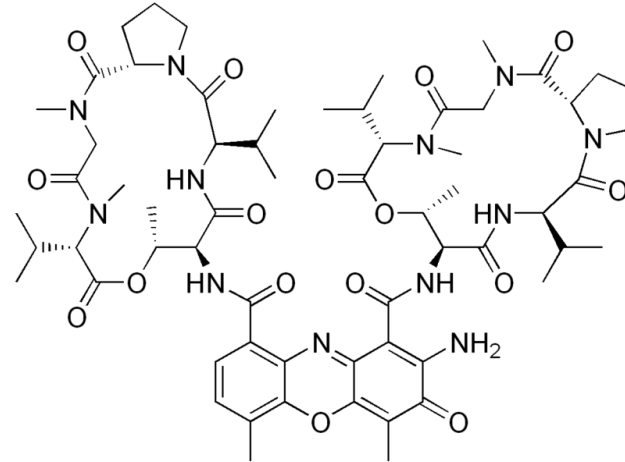
Mitomycin C.

S. caespitosis 1960

FDA approval 1974

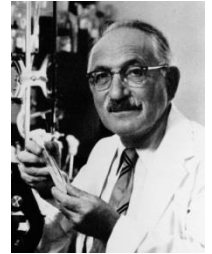


**Federico
Arcamone**
Naxospharma
Milan

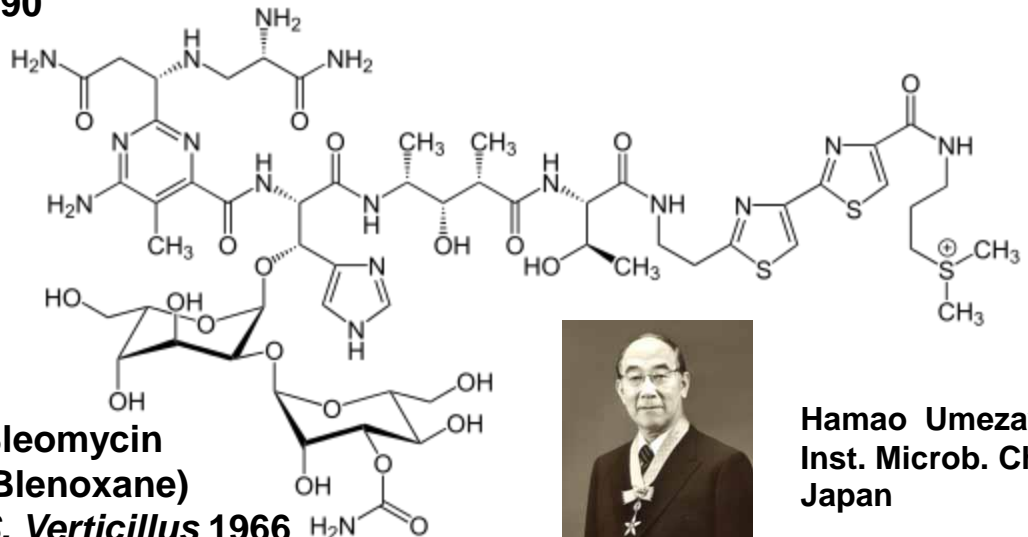


Dactinomycin (Actinomycin D)

S. antibioticus 1940; FDA approval 1964



**Selman
Waksman**
Rutgers Univ.



**Bleomycin
(Blenoxane)**

S. Verticillus 1966

FDA approval 1973



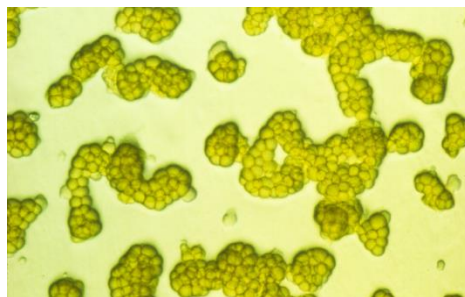
Hamao Umezawa
Inst. Microb. Chem.
Japan

EPOTHILONES FROM SLIME MOLDS (MYXOBACTERIA)

Hofle and Reichenbach. In: *Anticancer Agents from Natural Products*. Cragg, Kingston, and Newman, D. J., (Eds.), Second Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, 513-573 (<http://www.crcnetbase.com/isbn/9781439813829>)



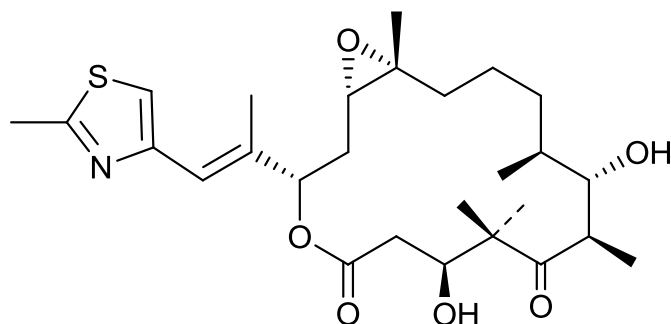
Gerhard Hofle & Hans Reichenbach, Braunschweig, Germany



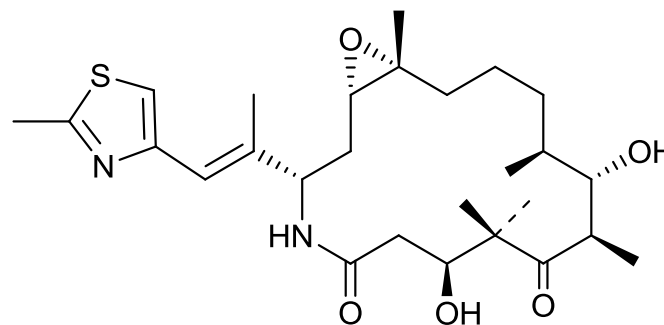
***Sorangium cellulosum*
Hans Reichenbach**



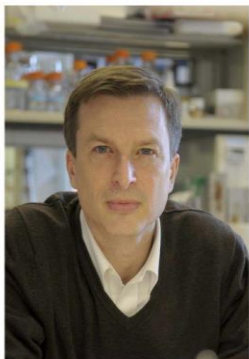
Eight epothilone analogs have been introduced into cancer clinical studies



Epothilone B (patupilone, Novartis) in phase III clinical trials for ovarian cancer



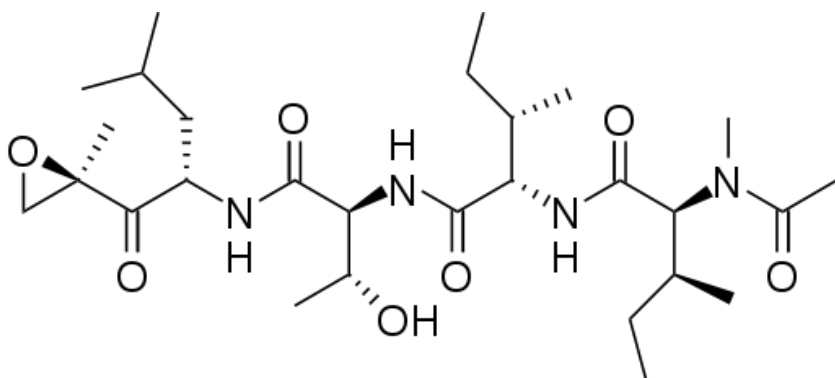
Epothilone B-Lactam (Ixabepilone, Ixempra) FDA approved for treatment of advanced and metastatic breast cancer resistant to taxanes and anthracyclines. 2007



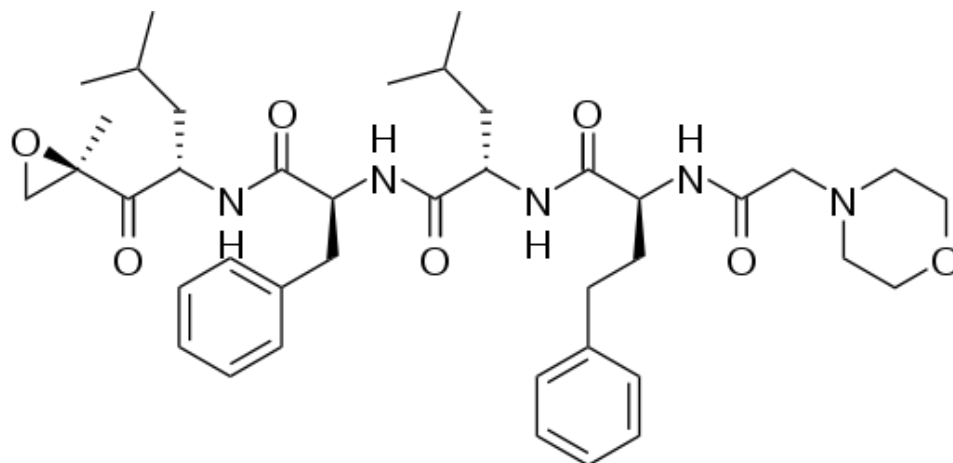
Craig Crews

EPOXOMICIN TO CARFILZOMIB

Kim & Crews, Nat. Prod. Rep., 2013, 30, 600-604



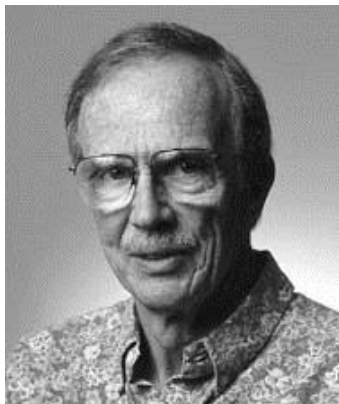
Epoxomicin isolated from an *Actinomycete* strain 1992.



**Carfilzomib (Kyprolis): Synthesis 1999.
Potent proteasome inhibitor.
FDA approval for treatment of multiple
myeloma in 2012.**

CYANOBACTERIA – A CONTINUING SOURCE OF PROMISING DRUG LEADS

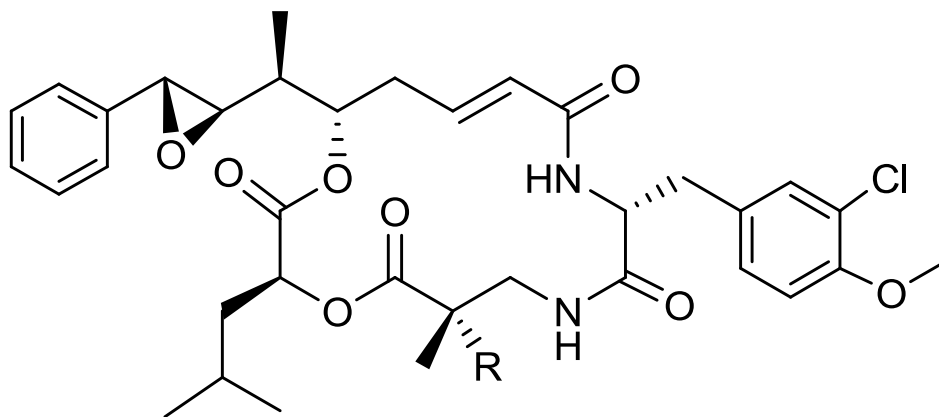
Tan, *Drug Discov. Today*, 2013, 18, 863-71; Nunnery, Mevers and Gerwick, *Curr. Opin. Biotechnol.*, 2010, 21, 787-93



Dick Moore
A pioneer in cyanobacterial drug discovery



Nostoc species



Cryptophycin A (Cryptophycin 1): R = H
Cryptophycin 52 (LY355703): R = CH₃



Bill Gerwick

Al-awar and Shih. In: *Anticancer Agents from Natural Products*. Cragg, Kingston, and Newman, (Eds.), Second Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, 219-240 (<http://www.crcnetbase.com/isbn/9781439813829>)
Cryptophycin 52 entered Phase II Clinical Trials but dropped due to toxicity and lack of efficacy.



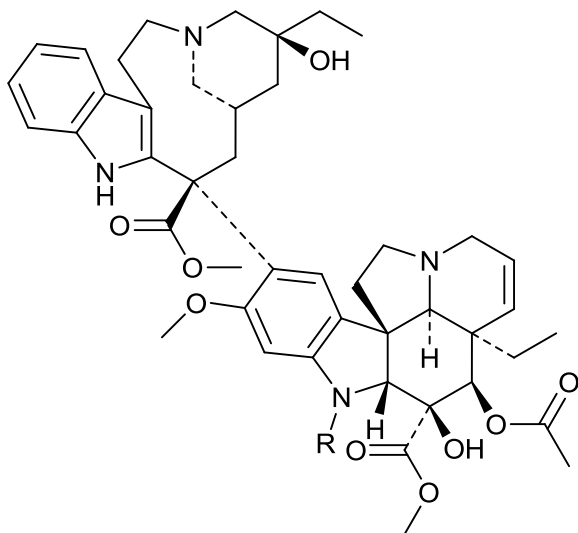
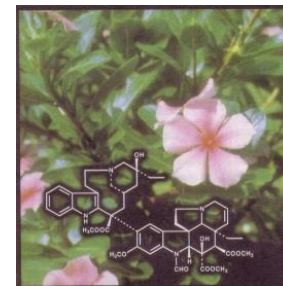
Gordon Svoboda

THE VINCA ALKALOIDS A KEY DISCOVERY FROM *CATHARANTHUS ROSEUS*

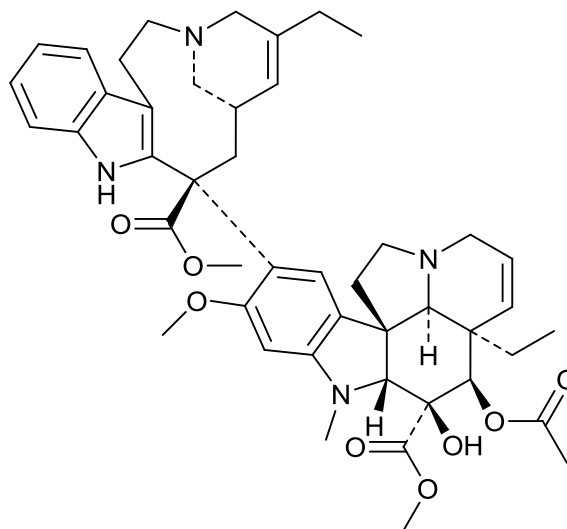
Roussi, Guéritte and Fahy In:
Anticancer Agents from Natural
Products. Cragg, Kingston, and
Newman, D. J., (Eds.), Second Edition,
CRC Press, Taylor & Francis Group,
Boca Raton, Florida, 2012, 177-198



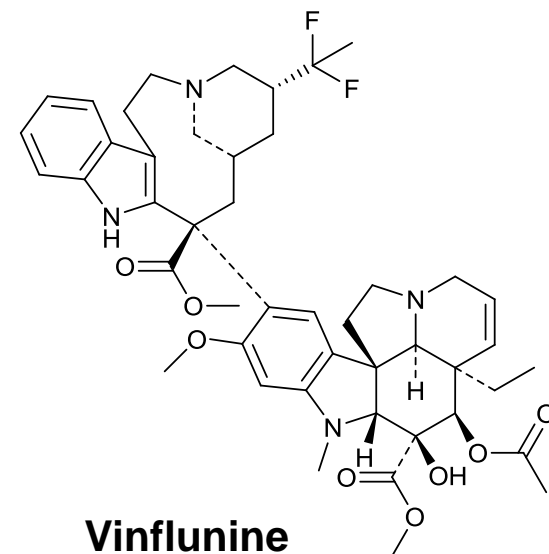
Pierre Potier, CNRS, France



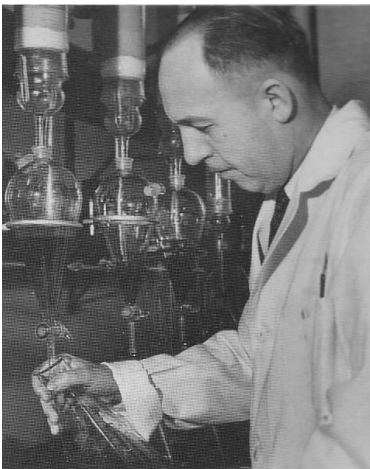
Vinblastine: R = CH₃ 1959
Velban FDA approval 1965
Vincristine: R = CHO 1961
FDA approval 1963



Vinorelbine (Navelbine)
Semisynthetic. Potier group
FDA approved 1994

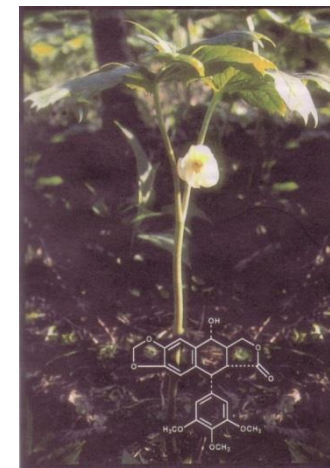


Vinflunine
Semisynthetic
EMA approved 2009



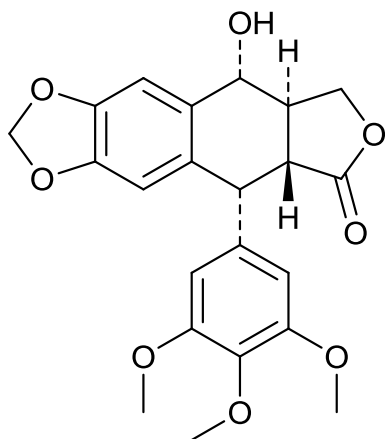
SEMISYNTHETIC ANALOGS OF PODOPHYLLOTOXIN ISOLATED FROM MEDICINAL *PODOPHYLLUM* SPECIES

Lee and Xiao In: Anticancer Agents from
Natural Products. Cragg, Kingston, and
Newman, D. J., (Eds.), Second Edition, CRC
Press, Taylor & Francis Group, Boca Raton,
Florida, 2012, 95-122.

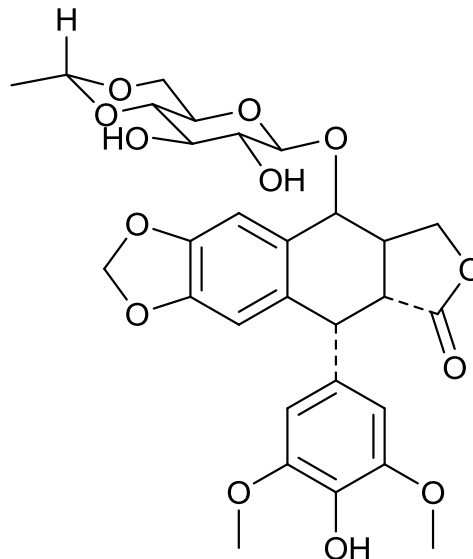


Jonathon Hartwell

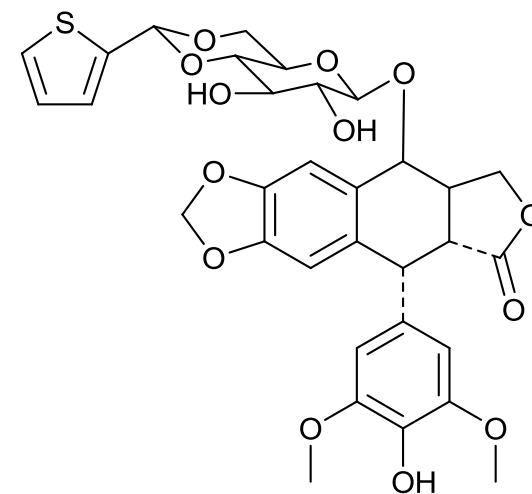
*Podophyllum
peltatum*



Podophyllotoxin
Structure reported in
1951 by
Hartwell and Schrecker



Etoposide. Semisynthesis,
Sandoz, 1966.
FDA approval 1984

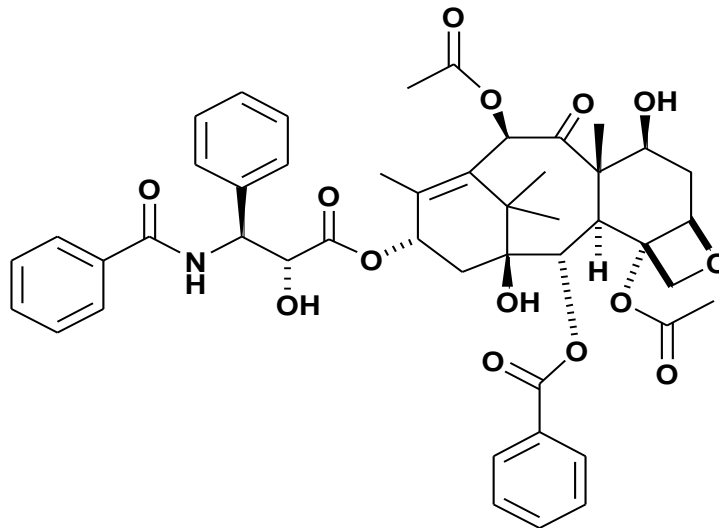


Teniposide (Vumon).
Semisynthesis 1967
FDA approval 1992

TAXOL®. MULTIDISCIPLINARY INTERNATIONAL COLLABORATION



Pacific Yew
Taxus brevifolia



Arthur Barclay, USDA
First bark collection, 1962

Bristol Myers Squibb/NCI CRADA 1989
FDA approval 1992 (ovarian); 1994 (breast)



**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



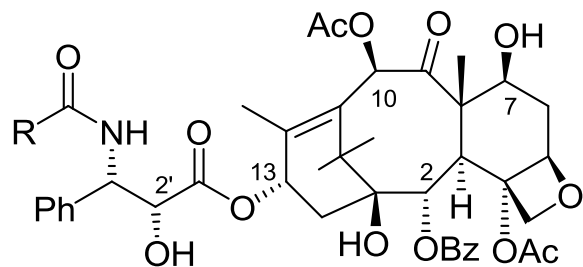
**Pierre Potier,
CNRS, France.**
Pioneered
semisynthesis
from 10-deacetyl
baccatin isolated
from leaves of *T.
baccata*. 1988



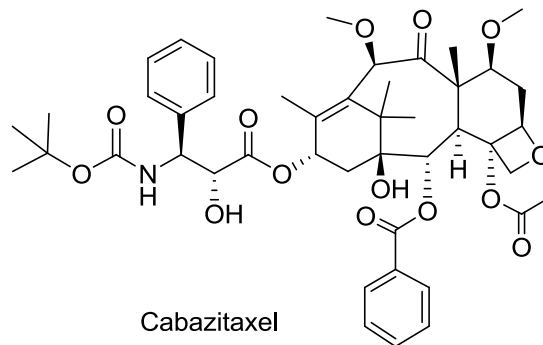
Eric Rowinsky
Johns Hopkins U.
Efficacy in
refractory ovarian
cancer. 1989

TAXOL®: A CONTINUING DEVELOPMENT PROCESS

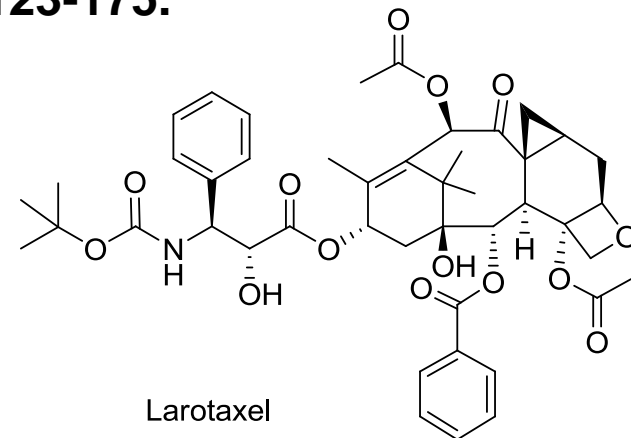
Kingston, In: Anticancer Agents from Natural Products. Cragg, Kingston, and Newman, (Eds.), 2nd Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, Ch. 6, pp. 123-175.



Paclitaxel R=Ph
Docetaxel R=CMe₃



Cabazitaxel



Larotaxel

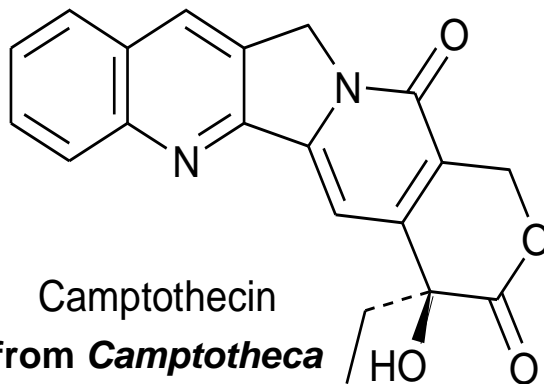
- Treatment of breast, ovarian and non small cell lung cancers, Kaposi sarcoma. 2,014 clinical trials ongoing (www.clinicaltrials.gov; July, 2014).
- Docetaxel: Similar treatment profile, but easier to formulate/administer. Potier, CNRS; Rhône-Poulenc Rorer (now Sanofi-Aventis). 1,717 clinical trials ongoing (July, 2014). FDA approval 1996.
- Cabazitaxel and an albumin-stabilized nanoparticle formulation of paclitaxel, Abraxane® (nab-paclitaxel, ABI-007) are also approved. FDA approvals: 2010 and 2012, respectively
- 4 other taxanes (e.g., larotaxel) in Phase III clinical trials. Five analogs and five new formulations are in Phase II and I trials. 14 in preclinical development
- Low-dose paclitaxel seems promising in treating non-cancer diseases, such as skin disorders, renal and hepatic fibrosis, inflammation, axon regeneration, limb salvage, and coronary artery restenosis. (Zhang et al., Drug. Des. Devel. Ther., 2014, 8:279-84).

CAMPTOTHECIN AND SEMISYNTHETIC ANALOGS

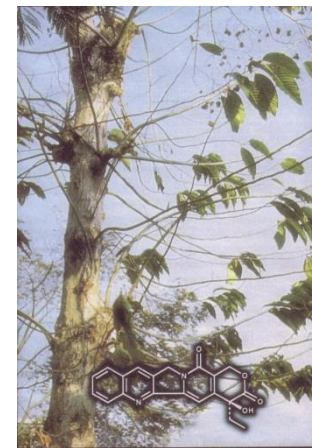
Rahier, Thomas and Hecht In: Anticancer Agents from Natural Products.
Cragg, Kingston, and Newman, (Eds.), 2nd Edition, CRC Press, Taylor &
Francis Group, Boca Raton, Florida, 2012, Ch. 2, pp. 5-25.



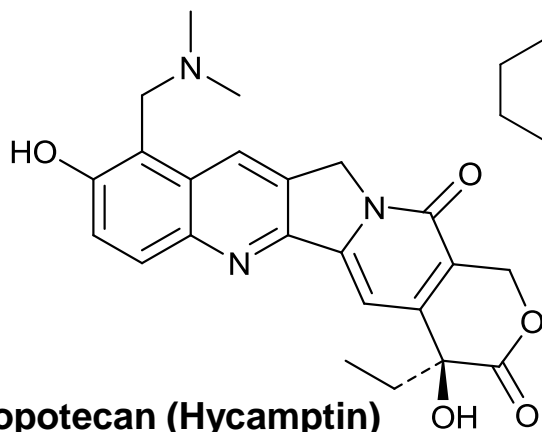
Mansukh Wani and
Monroe Wall
(Photograph: J. W.
Crawford, RTI)



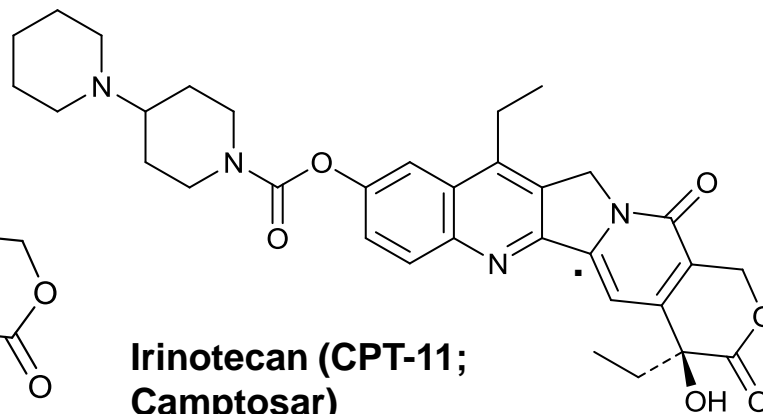
Camptothecin
Isolation from *Camptotheca
acuminata* reported 1966



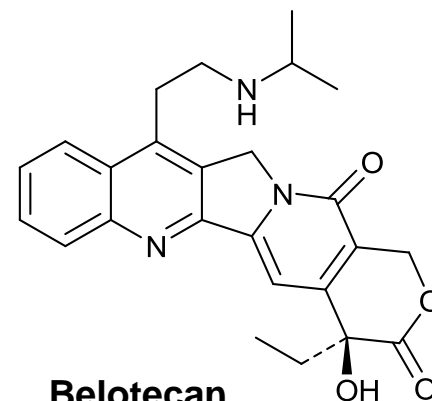
*Camptotheca
acuminata*



Topotecan (Hycamptin)
Semisynthesis 1991
FDA approval 1996



Irinotecan (CPT-11;
Camptosar)
Semisynthesis 1991
FDA approval 1996



Belotecan
Semisynthesis 2000

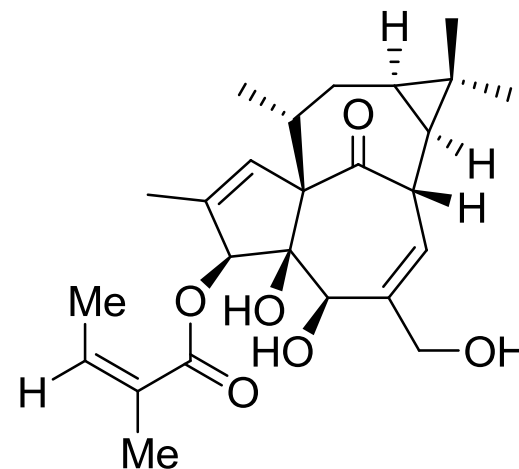
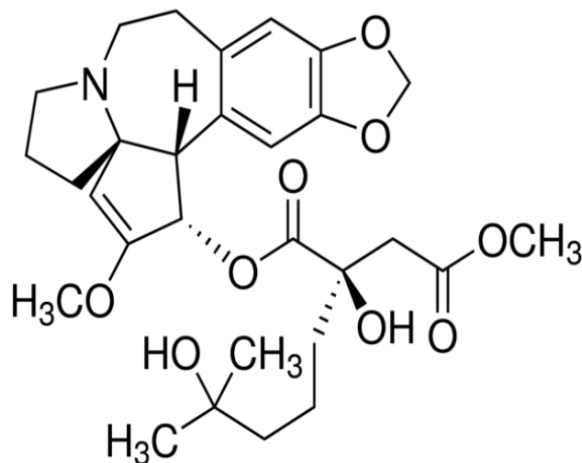
HOMOHARRINGTONINE AND INGENOL METABUTATE

Kantarjian et al., Homoharringtonine/omacetaxine mepesuccinate: the long and winding road to food and drug administration approval. *Clin. Lymphoma Myeloma Leuk.*, 2013,13(5), 530-533; Nazha A, Kantarjian H, Cortes J, Quintás-Cardama A. Omacetaxine mepesuccinate (synribo) - newly launched in chronic myeloid leukemia. *Expert Opin. Pharmacother.*, 2013, 14(14), 1977-1986.

Lebwohl et al., Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. *JAMA Dermatol.* 2013, 149(6), 666-70; Siller et al., PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. *Australas. J. Dermatol.*, 2009, 50(1), 16-22.



Richard Powell



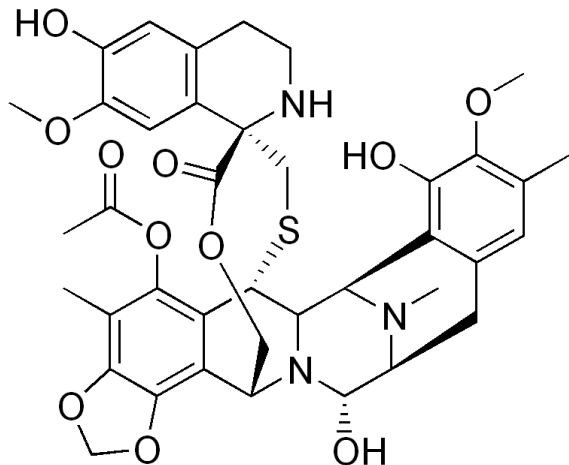
Homoharringtonine (Synribo; Omacetaxine)
Isolated from *Cephalotaxus harringtonia* by Powell USDA group. 1970
FDA approval for treatment of chronic myeloid leukemia. 2012

Ingenol metabutate (Picato)
Isolated from *Euphorbia peplus* 2004
FDA approval for treatment of actinic keratosis lesions. 2012

MARINE-DERIVED ANTICANCER DRUGS

ECTEINASCIDIN 743. TRABECTEDIN

Cuevas et al. In: Anticancer Agents from Natural Products. Cragg, Kingston, and Newman, (Eds.), 2nd Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, 291-316.



Ken Rinehart



Amy Wright



Carmen Cuevas
Pharmamar, Spain



Isolation from *Ecteinascidia turbinata* reported independently by Rinehart and Wright in 1990.

FDA granted orphan drug status for treatment of soft tissue sarcoma in 2004 and ovarian cancer in 2005.; in clinical trials against a range of other cancers including breast, ovarian, pancreatic and prostate.

ERIBULIN: Total Synthesis – Route to a Better Drug Candidate

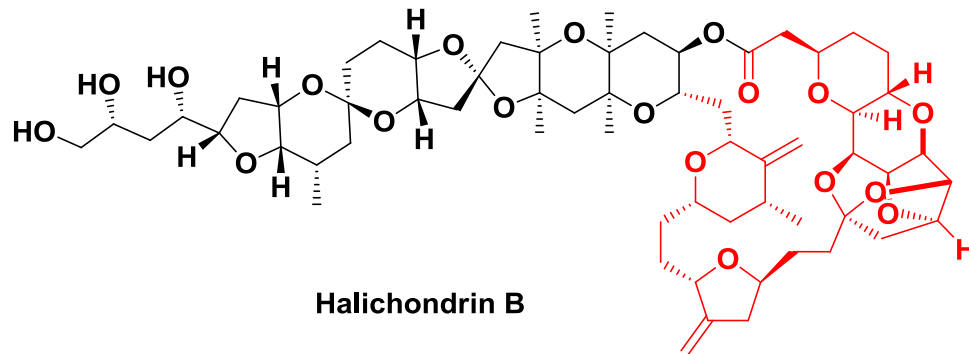
M. J. Yu, Y. Kishi, B. A. Littlefield, In: *Anticancer Agents from Natural Products*. Cragg, Kingston, and Newman, D. J., (Eds.), Second Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, pp. 317-345



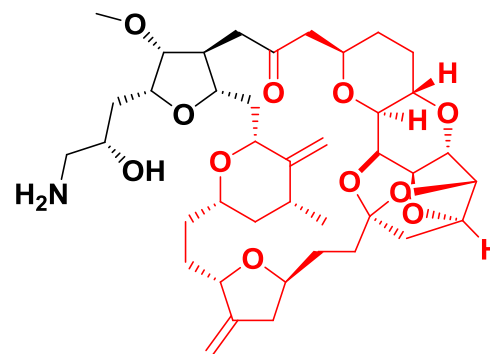
Murray Munro
U. Canterbury, NZ



Lissodendoryx sp.



Yoshito Kishi

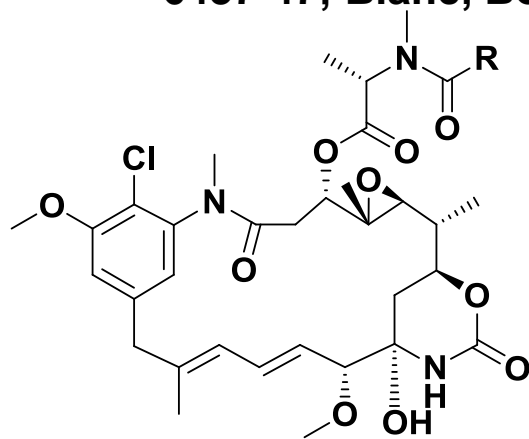


Halichondrin B (HB): Isolation from *Halichondria okadai* in 1985, and later from *Phakelia carteri*, *Axinella* sp. and a *Lissodendoryx* sp. off New Zealand. Following total synthesis of HB, eribulin was identified as the optimal candidate for clinical development. It was approved as Halaven by the FDA in 2010 for the treatment of refractory breast cancer. Currently in clinical trials against several other cancers, mainly in combination with other agents.

Maytansanoids. Targeted Delivery

Yu & Floss. In: Anticancer Agents from Natural Products. Cragg, Kingston, and Newman, (Eds.), 2nd Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, 407-27

LoRusso, Weiss, Guardino, Girish, and Sliwowski, Clin. Cancer Res., 2011, 17, 6437-47; Blanc, Bousseau, Caron, Carrez, Lutz, and Lambert, ibid, 6448-58



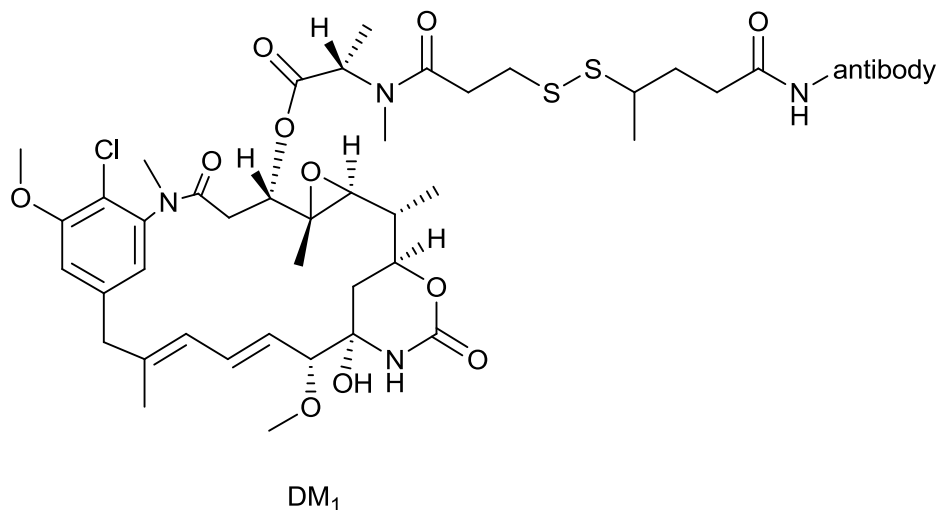
Morris Kupchan

Maytansine, R = CH₃

DM1, R = CH₂CH₂SH

DM4, R = CH₂CH₂C(CH₃)₂SH

Maytansine isolated in the 1960s by Morris Kupchan from *Maytenus buchanii* and *serrata*. Too toxic in clinical trials to develop further. Ansamitocins related to maytansine isolated from *Actinosynnema pretiosum* which is possibly endophytic to the original plant.



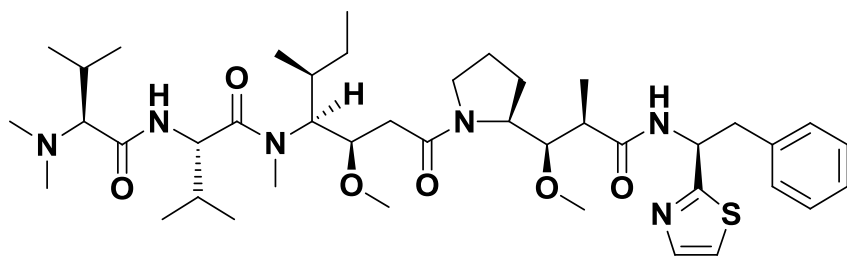
Trastuzumab (herceptin)-DM1 conjugate (Kadcyla) approved by FDA in Feb., 2013, for treatment for Her2+ late stage (metastatic) breast cancer.

Other DM1 Antibody Drug Conjugates (ADCs) are in Phase I and II clinical trials (breast, leukemias, lymphomas, gastric, small-cell lung)

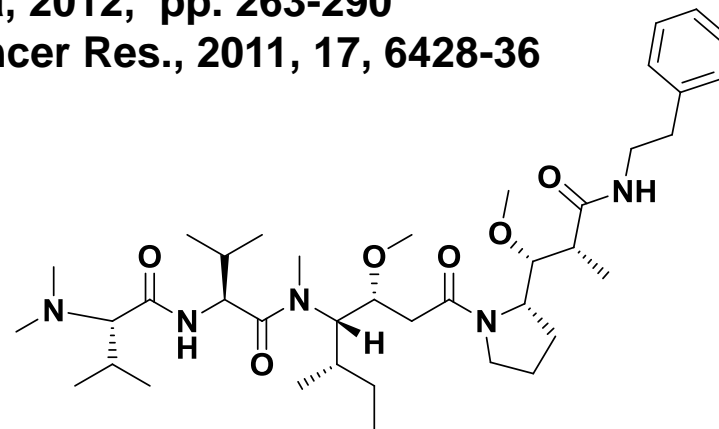
Dolastatins. Targeted Delivery

Flahive & Srirangam, In: Anticancer Agents from Natural Products. Cragg, Kingston, and Newman, D. J., (Eds.), 2nd Edition, CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012, pp. 263-290

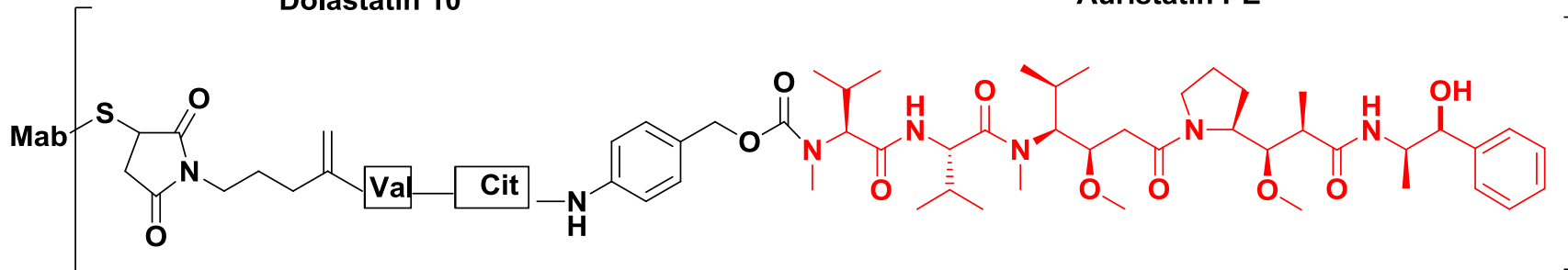
Katz, Janik, and Younes, Clin. Cancer Res., 2011, 17, 6428-36



Dolastatin 10



Auristatin PE



Brentuximab vedotin; Red color is momomethylauristatin E

Conjugation to the humanized anti-CD30 monoclonal antibody SGN-30 gives brentuximab vedotin (Adcetris[®]), directed against the CD30 antigen expressed on Hodgkin lymphoma and anaplastic large cell lymphoma. FDA approved , 2011.

ANTICANCER AGENTS FROM NATURAL PRODUCTS RECENT REVIEWS

**Basmadjian et al., Cancer wars: Natural products strike back.
Front. Chem., 2014, 2:20
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4013484/>)**

**Anticancer Agents from Natural Products. Cragg, Kingston, and
Newman, (Eds.), 2nd Edition, CRC Press, Taylor & Francis Group,
Boca Raton, Florida, 2012.
(<http://www.crcnetbase.com/isbn/9781439813829>)**

**Demain and Vaishnav. Natural products for cancer chemotherapy.
Microb. Biotechnol., 2011, 4 :687-699.**

**Cragg, Grothaus, and Newman, Impact of Natural Products on
Developing New Anti-Cancer Agents, Chem. Rev., 2009, 109: 3012-
3043.**

NEW FRONTIERS

Microbial Symbionts

- **Endophytic fungi**

Verma, Strobel et al., Chemical and functional diversity of natural products from plant associated endophytic fungi *Nat. Prod. Commun.*, 2009, 4, 1511-1532

Kharwa, Stierle et al., Anticancer compounds derived from fungal endophytes: their importance and future challenges. *Nat. Prod. Rep.*, 2011, 28, 1208-1228



Gary Strobel

- **Marine microbial symbionts**

Hentschel et al., Diversity, abundance and natural products of marine sponge-associated actinomycetes. *Nat. Prod. Rep.*, 2014, 31, 381-399

Crews et al., Scrutinizing the scaffolds of marine biosynthetics from different source organisms: Gram-negative cultured bacterial products enter center stage. *J. Nat. Prod.*, 2014, 77, 690-702

Haygood, Schmidt et al., Genome streamlining and chemical defense in a coral reef symbiosis. *Proc. Natl. Acad. Sci.*, 2012, 109, 20655-60.

Hentschel, Piel et al., Genomic insights into the marine sponge microbiome. *Nat. Rev. Microbiol.*, 2012, 10, 641-654

- **Insect microbial symbionts**

Currie, Clardy et al., Bacterial symbionts in agricultural systems provide a strategic source for antibiotic discovery. *J. Antibiot.*, 2014, 67, 53-58

Crawford and Clardy, Bacterial symbionts and natural products. *Chem. Commun. (Camb)*, 2011, 47, 7559-7566

Clardy, Currie et al., Chemical analyses of wasp-associated streptomyces bacteria reveal a prolific potential for natural products discovery. *PLoS One*. 2011 Feb 22;6(2):e16763.



Jon Clardy

GENOME MINING

Journal of Industrial Microbiology & Biotechnology

Volume 41, Issue 2, February 2014

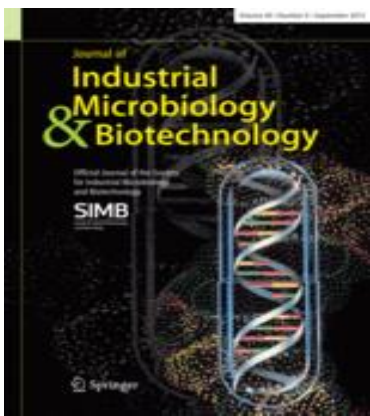
Special Issue: Microbial Genome Mining

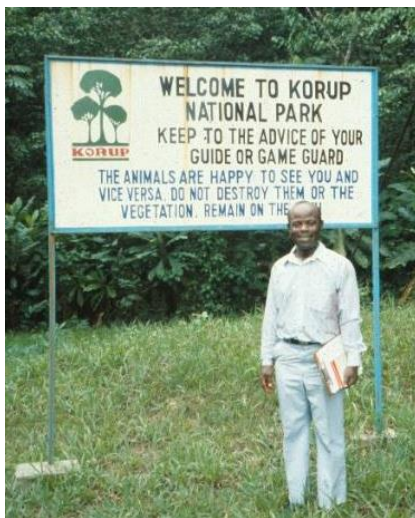
Dedicated Sir David Hopwood

26 articles : Bachmann, Balz et al., Microbial genome mining for accelerated natural products discovery: is a renaissance in the making? : 175-84; Demain , Importance of microbial natural products and the need to revitalize their discovery. : 185-201; Jensen , Fenical , Moore et al., Challenges and triumphs to genomics-based natural product discovery. : 203-9; Diminic et al., Evolutionary concepts in natural products discovery: what actinomycetes have taught us. :211-7; Aigle , Spiteller, Challis et al., Genome mining of *Streptomyces ambofaciens*. : 251-63; Challis , Exploitation of the *Streptomyces coelicolor* A3(2) genome sequence for discovery of new natural products and biosynthetic pathways. :219-32



David Hopwood
John Innes Center
Norwich, UK





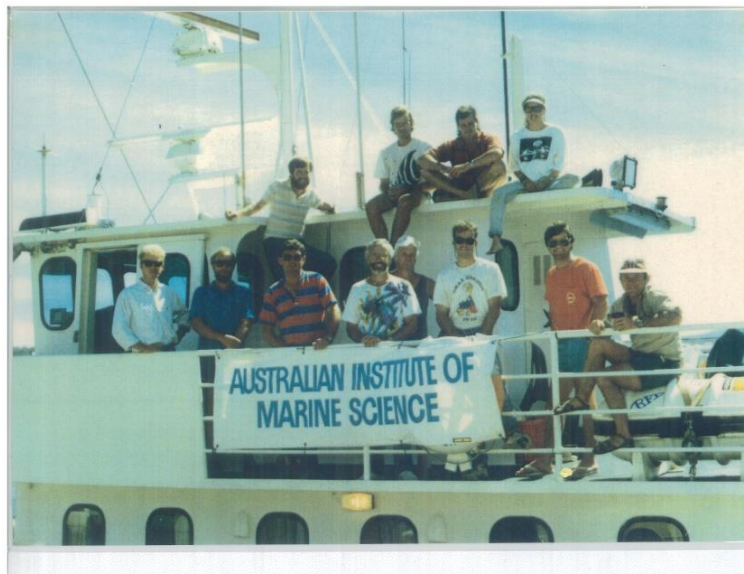
Johnson Jato, Cameroon

DRUG DISCOVERY AND



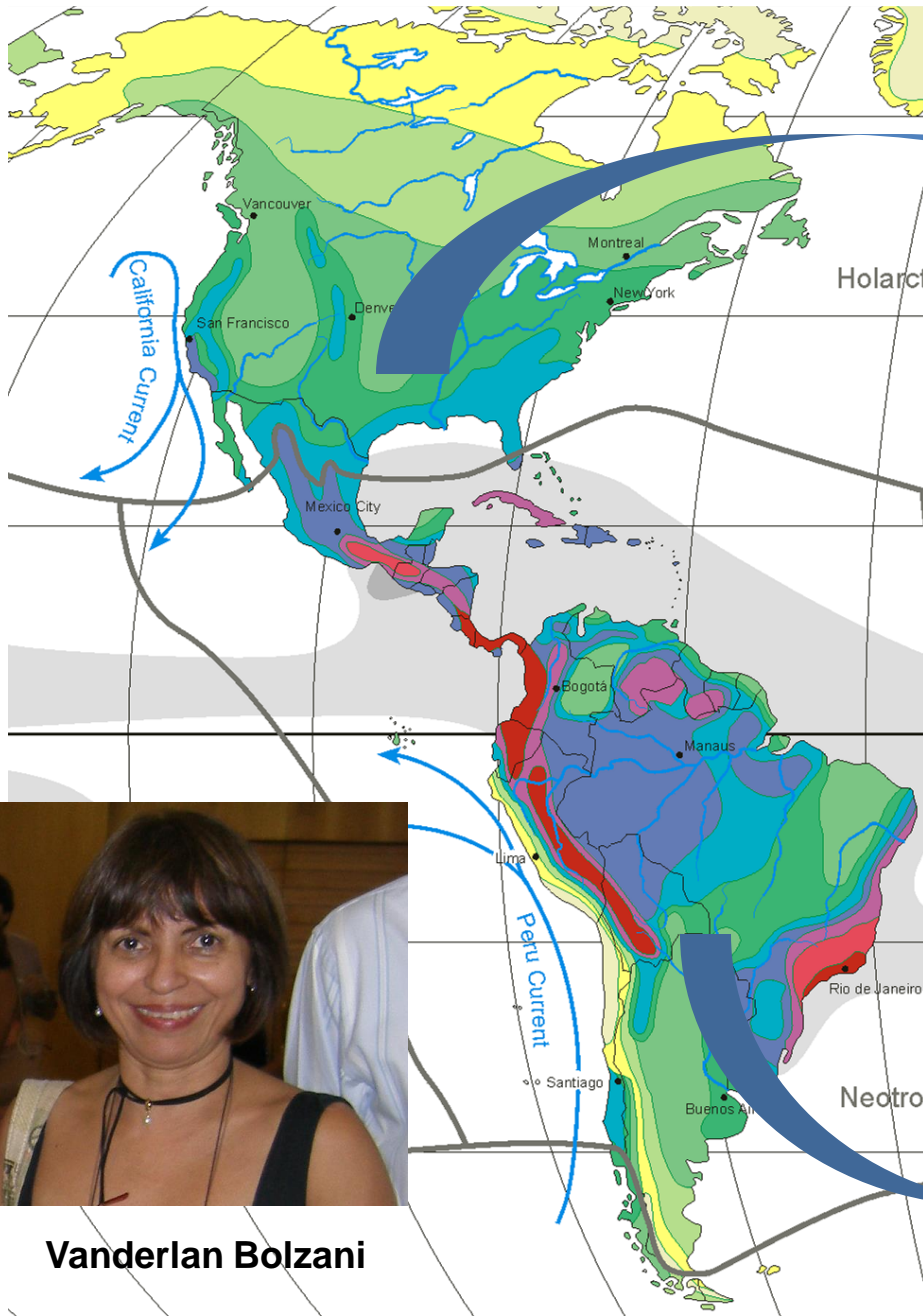
Ahsana Dar and Iqbal Choudhary & colleagues, Univ. Karachi, Pakistan

INTERNATIONAL COLLABORATION



Leticia Costa Latufo, Odorico DeMoraes and Claudia Pessoa, Federal Univ. Ceara, Fortaleza, Brazil. Collaboration with many Brazilian groups in antitumor screening





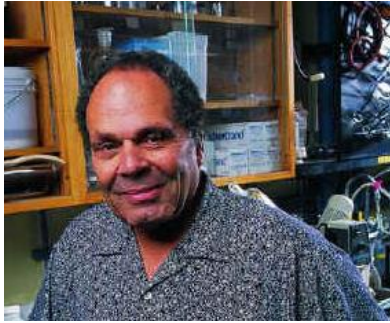
Taxol®

Huge untapped Brazilian resources – how many new drugs await discovery?



Vanderlan Bolzani

COLLABORATION – THE KEY



Phil Crews, UCSC



Bill Gerwick, Scripps
Oceanographic Inst.



David Sherman, U.
Wisconsin, Madison



Lohi Matainaho
University of Papua
New Guinea
Major Collaborator
With
Several groups



Ray Andersen
U. Br. Columbia



Chris Ireland, Louis Barrows (U. Utah)
and Lohi Matainaho

