A CONTRIBUIÇÃO DO PRODUTOS NATURAIS À FARMACOLOGIA

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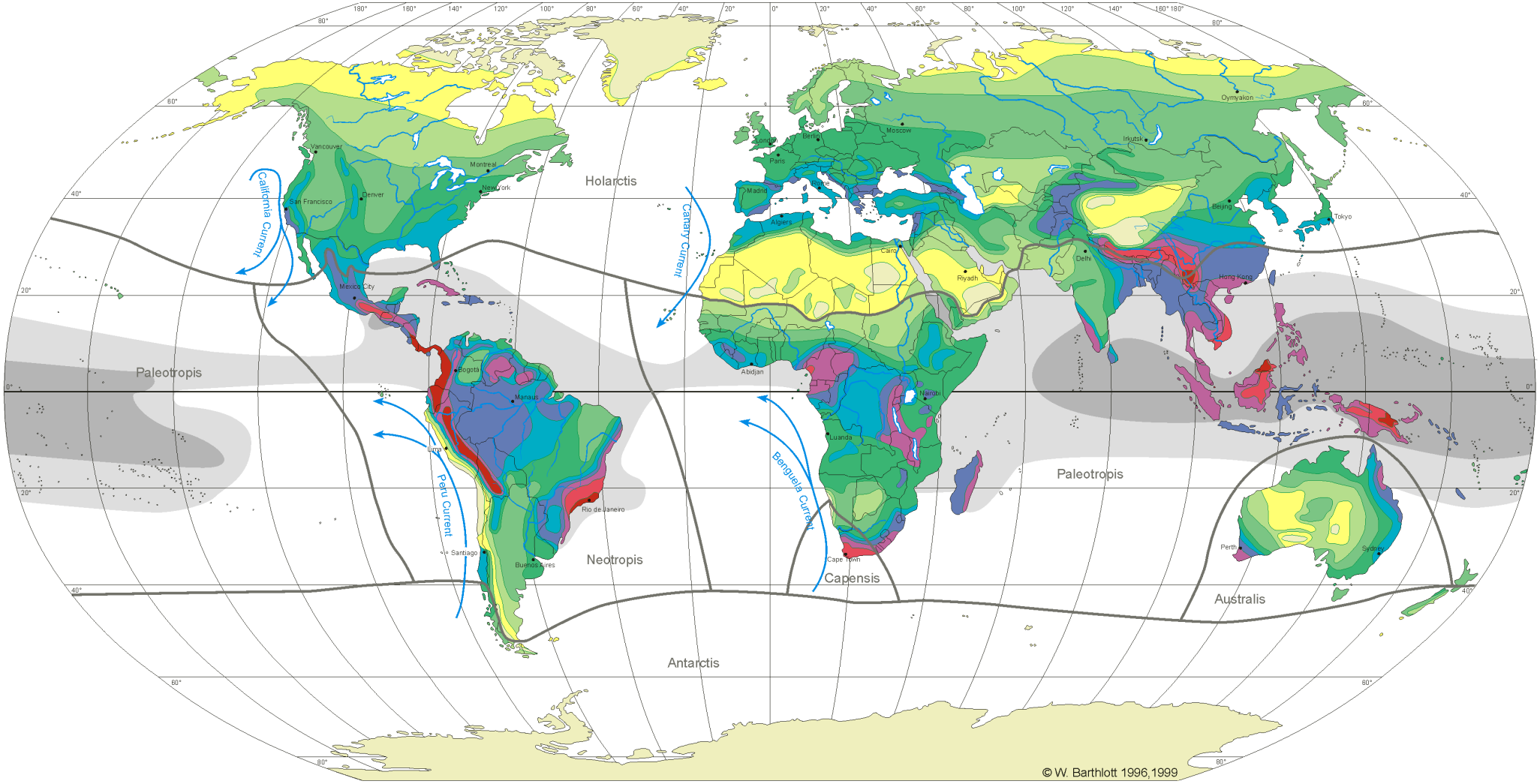
GLOBAL BIODIVERSITY: SPECIES NUMBERS OF VASCULAR PLANTS



Robinson Projection
Standard Parallels 38°N und 38°S

Diversity Zones (DZ): Number of species per 10 000km²

- DZ 1 (<100)
- DZ 2 (100 - 200)
- DZ 3 (200 - 500)
- DZ 4 (500 - 1000)
- DZ 5 (1000 - 1500)
- DZ 6 (1500 - 2000)
- DZ 7 (2000 - 3000)
- DZ 8 (3000 - 4000)
- DZ 9 (4000 - 5000)
- DZ 10 (≥ 5000)

Capensis floristic regions

sea surface temperature

- >29°C
- >27°C

cold currents

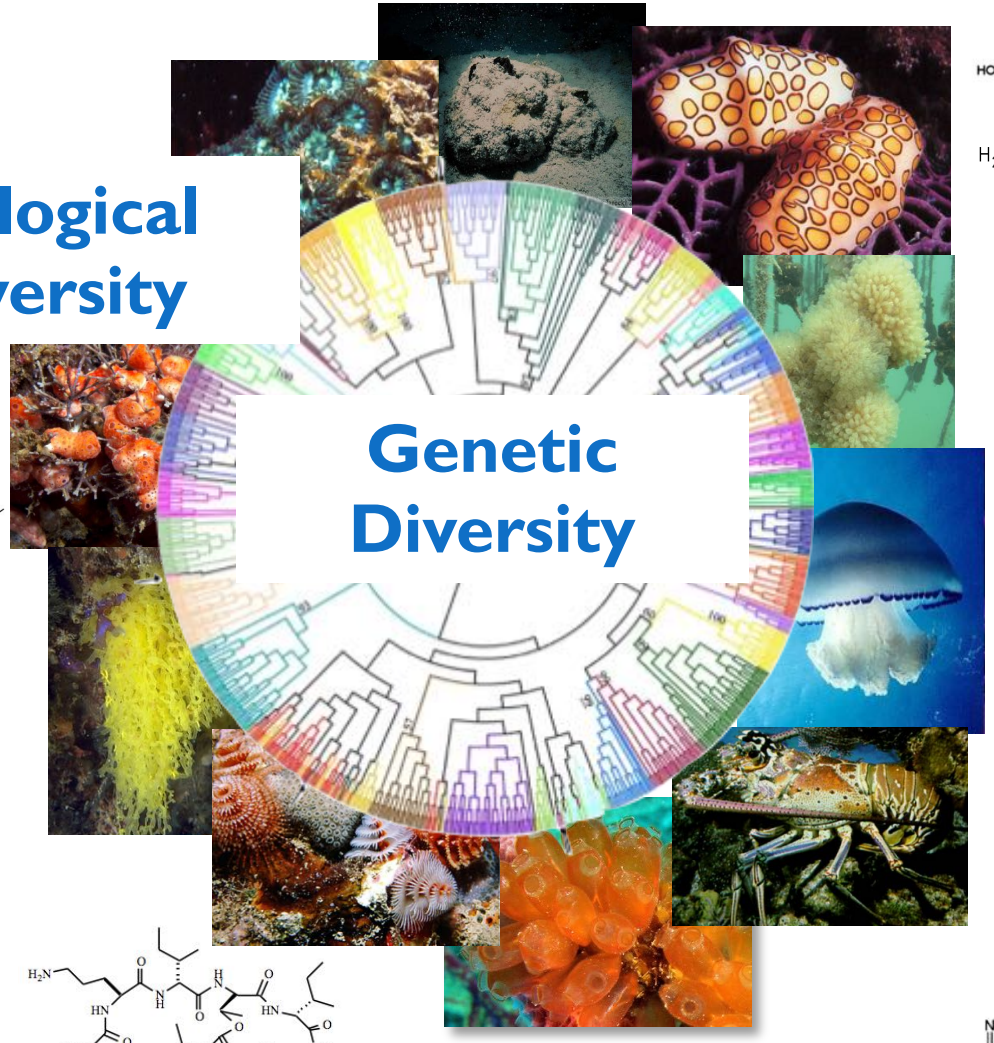
W. Barthlott, N. Biedinger, G. Braun, F. Feig, G.Kier, W. Lauer & J. Mutke 1999
modified after
W. Barthlott, W. Lauer & A. Placke1996
Department of Botany and Geography
University of Bonn
German Aerospace Research Establishment, Cologne
Cartography: M. Gref
Department of Geography University of Bonn

A very sophisticated synthetic lab!

Chemical Diversity

Biological Diversity

Genetic Diversity



INDUSTRIES FROM BIODIVERSITY...

Biomonitoring

Biological Control

Ethnobotanicals

Phytomedicines

Horticulture

Pharmaceuticals

Biofuels

Cosmeticals

Personal care

Bioremediation

Ecotourism

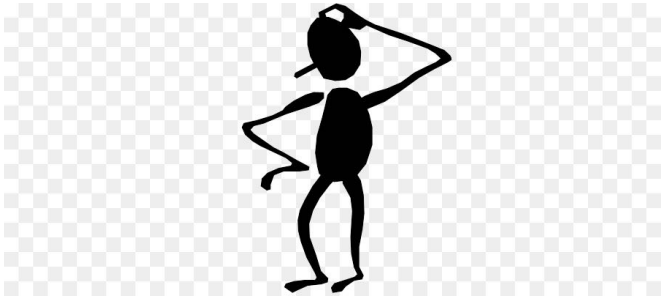
Biomimetics

Crop protection

Agriculture

Restoration

Como e quando a humanidade começou a usar os produtos naturais na terapêutica?



PRÉ-HISTÓRIA:

- Não há como determinar exatamente quando as plantas passaram a ser utilizadas para tratar doenças
- Provavelmente descobertas acidentais marcam o início do conhecimento popular
- Primeiras evidências: Neanderthal enterrado a 60.000 anos com plantas de uso medicinal (análise através do pólen)

PRIMEIROS REGISTROS:

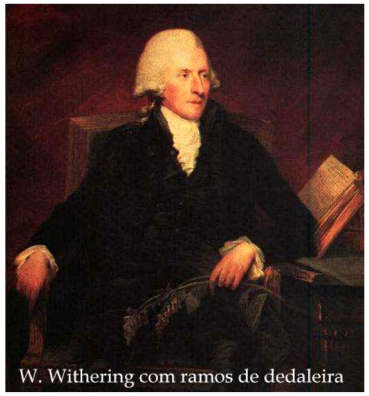
- Sumerianos registraram o uso de numerosos remédios preparados a partir de plantas a 4000 anos
- Egito antigo – Papiro de Ebers (3500 anos)
- China antiga – 1a. Farmacopéia publicada no ano 1600 com milhares de preparações vegetais atribuídas ao Imperador Shen-nung que viveu a mais de 4500 ano
- Na índia, plantas medicinais descritas no versos sagrados Rig-Veda. Base da medicina Ayurvedica

ROMA E GRÉCIA ANTIGAS

- Hippocrates (460-377 B.C.), conhecido como o pai da medicina, utilizava várias plantas medicinais nos seus tratamentos
- O médico romano Discoriades (1o. Século D.C) escreveu *De Materia Medica,* uma coleção de livros que contém mais de 600 espécies de plantas medicinais. Foi utilizada como referência médica por mais de 1500 anos.

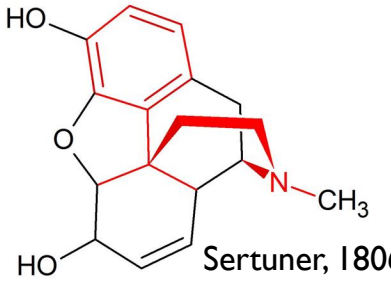
O CAMINHO PARA A MEDICINA MODERNA

- Comprovação científica do uso popular
- Algumas preparações passam a ser prescritas
- William Withering foi o primeiro cientista a investigar cientificamente um remédio popular
- Estudos (1775-1785) com *Digitalis* sp para o tratamento da insuficiência cardíaca congestiva


W. Withering com ramos de dedaleira

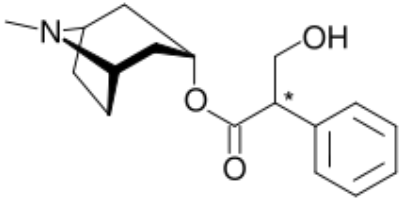
SÉCULO 19

- Começam os estudos de purificação dos princípios ativos das plantas medicinais

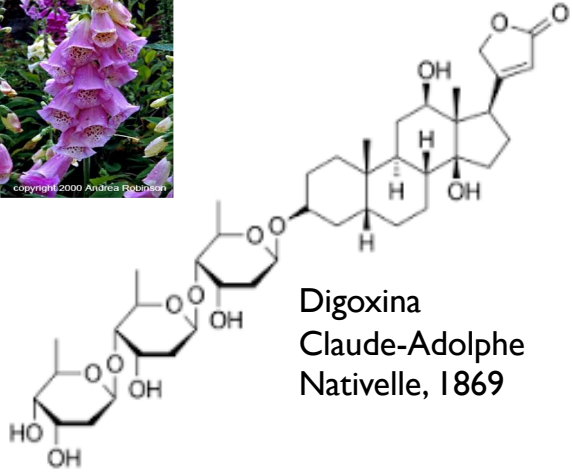


Sertuner, 1806

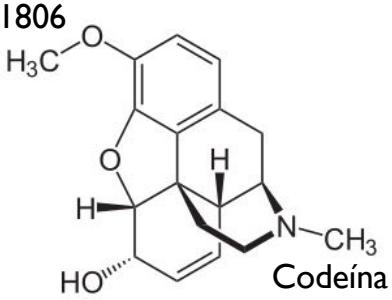
Morfina



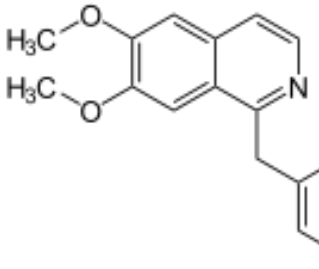
Atropina
Mein, 1831



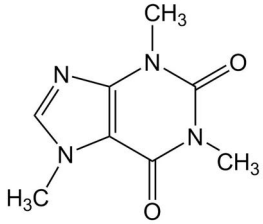
Digoxina
Claude-Adolphe
Nativelle, 1869



Codeína
Pierre-Jean Robiquet, 1824.



Papaverina
George Merck, 1848



Caféína,
Runge, 1820

SÉCULO 20:

- O uso de extratos de plantas diminui com o avanço da medicina alopática
- Ainda assim as plantas medicinais ainda contribuem para um número significativo das prescrições
  - Política Nacional de Plantas Medicinais e Fitoterápicos (2006)
  - Programa Fármacias Vivas
- Muitas moléculas sintéticas são inspiradas nas moléculas naturais

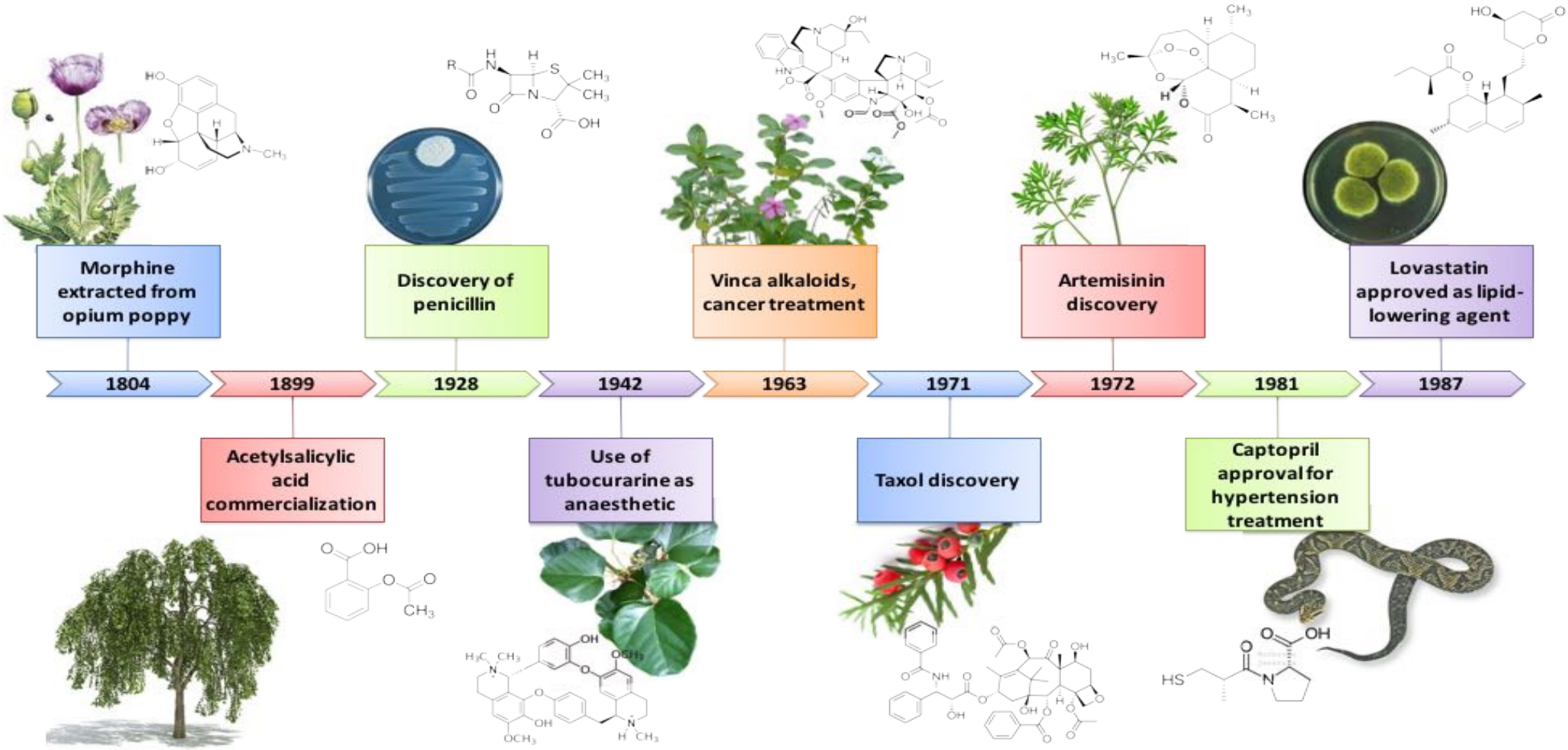
O IMPACTO DOS PRODUTOS NATURAIS NA P&D DE MEDICAMENTOS

- Os PN correspondem 60% do mercado farmacêutico.
- 70% dos antibióticos em uso clínico são PN ou derivados (U$ 32 bilhões)
- Novas entidades químicas (52% são PN ou derivadas de PN);
- PN e fármacos relacionados são usados para tratamento de 80% de todas as doenças (48/55);
- 84 de 150 das drogas mais prescritas são PN ou fármacos relacionados.

Singh and Macdonalds, 2010. Drug Discovery Today 15 (17/18). Chin *et al*., 2006. AAPS Journal 8 (2): article 28

EXEMPLOS DE FÁRMACOS DE ORIGEM NATURAL

- Analgésicos:
  - Aspirina (*Salix* spp./Europa); Morfina, codeína (*Papaver somniferum*/Mesopotâmia)
- Asma:
  - Efeddrine: *Ephedra sinica*/China; Cardiotônicos digoxina (*Digitalis purpurea*/UK-Europe)
- Malária:
  - Quinina: *Cinchona* spp./Amazonia; Artemisinina: *Artemisia annua*/China
- Câncer:
  - Paclitaxel (Taxus briviflora); Alcalóides da vinca (*Catharanthus roseus*)
- Hipolipidêmicos
  - Estatinas (*Penicillium citrinum*)
- Hipoglicemiantes
  - Metformina (*Galega officinalis*)


Morphine extracted from opium poppy
1804
Acetylsalicylic acid commercialization
1899
Discovery of penicillin
1928
Use of tubocurarine as anaesthetic
1942
Vinca alkaloids, cancer treatment
1963
Taxol discovery
1971
Artemisinin discovery
1972
Captopril approval for hypertension treatment
1981
Lovastatin approved as lipid-lowering agent
1987

The Gila Monster and the development of Byetta®

Heloderma suspectum (Helodermatidae)

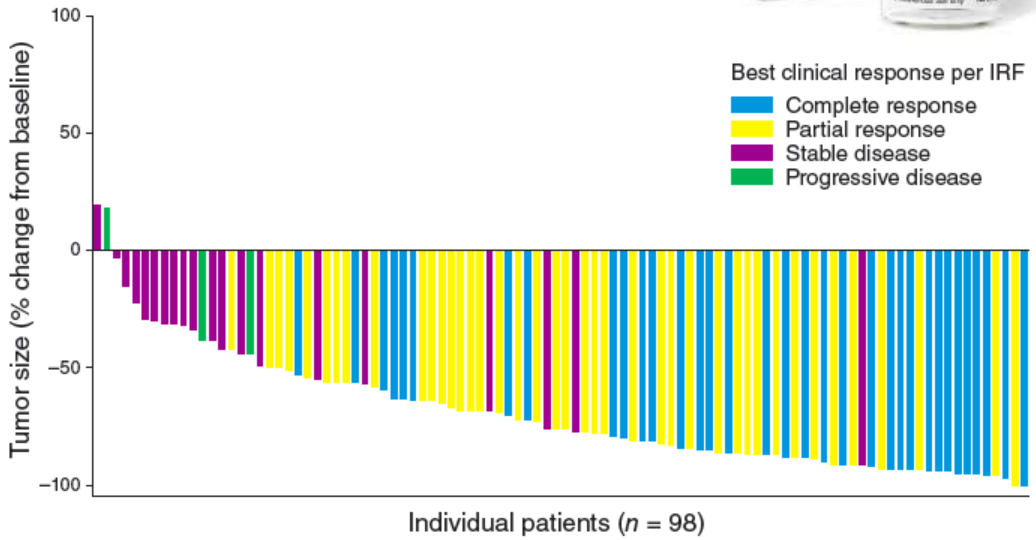
Exenatide (INN, marketed as Byetta) is one of a new class of medications (incretin mimetics) approved by FDA (Apr 2005) for the treatment of diabetes mellitus type 2)

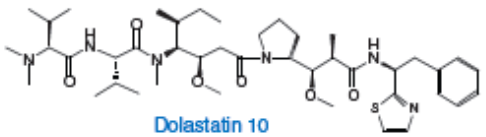
39-amino-acid peptide

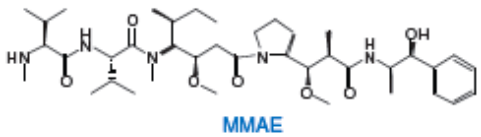
D. Drucker, J. Buse, K. Taylor, D. Kendall, M. Trautmann, D. Zhuang, L. Porter. The Lancet, 372, 2008, 1240–1250

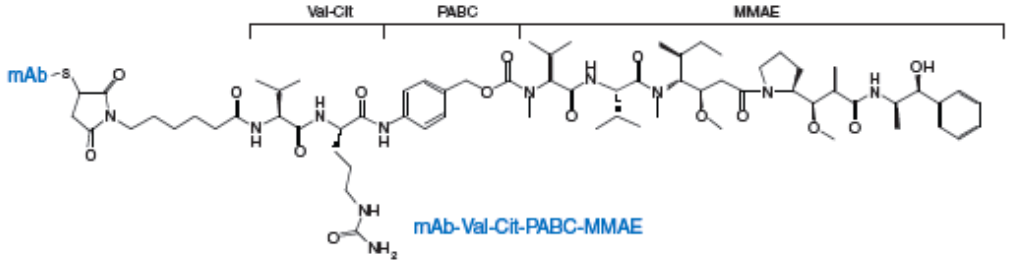
ADCETRIS®

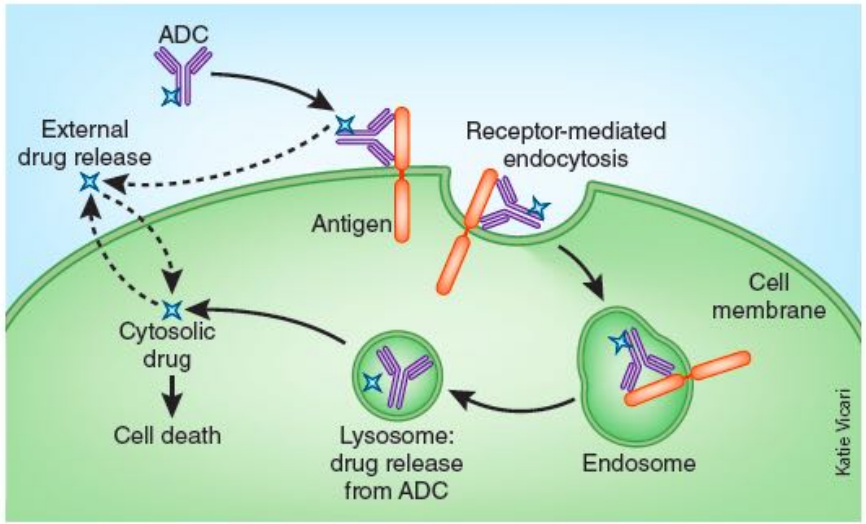
brentuximab vedotin | for injection











Senter & Sievers, 2012. Nature Biotechnology, 30, 631.

The Nobel Prize in Physiology or Medicine 2015

Ill. N. Elmehed. © Nobel Media AB 2015.

William C. Campbell

Prize share: 1/4

Ill. N. Elmehed. © Nobel Media AB 2015.

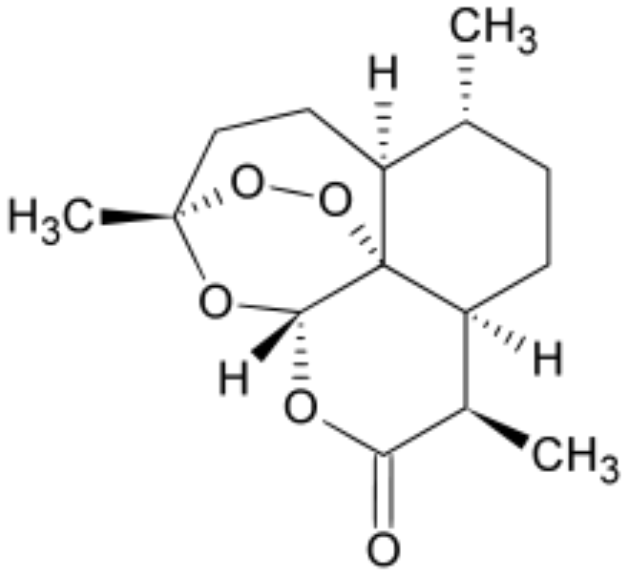
Satoshi Ōmura

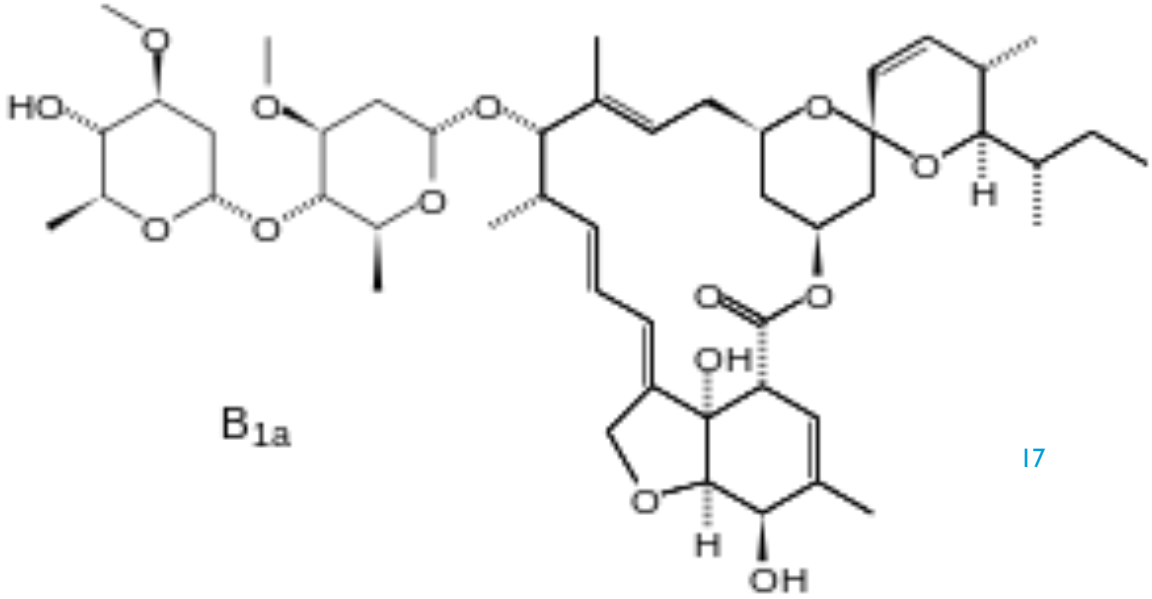
Prize share: 1/4

Ill. N. Elmehed. © Nobel Media AB 2015.

Youyou Tu

Prize share: 1/2





B_{1a}

JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp

Review

Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019

David J. Newman* and Gordon M. Cragg

Cite This: *J. Nat. Prod.* 2020, 83, 770–803

Read Online

Table 1. Codes Used in Analyses

code	brief definition/year
B	biological macromolecule, 1997
N	unaltered natural product, 1997
NB	botanical drug (defined mixture), 2012
ND	natural product derivative, 1997
S	synthetic drug, 1997
S*	synthetic drug (NP pharmacophore), 1997
V	vaccine, 2003
/NM	mimic of natural product, 2003

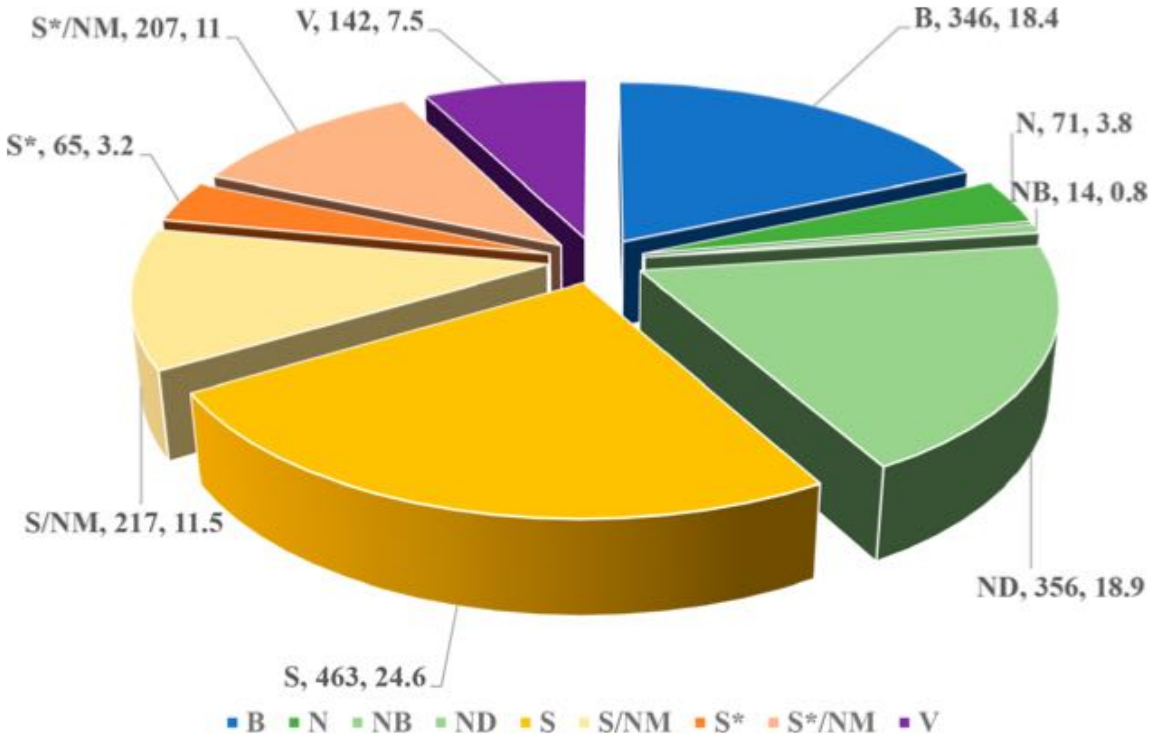


Figure 1. All new approved drugs 01JAN81 to 30SEP19; n = 1881.

ALL NEW APPROVED DRUGS

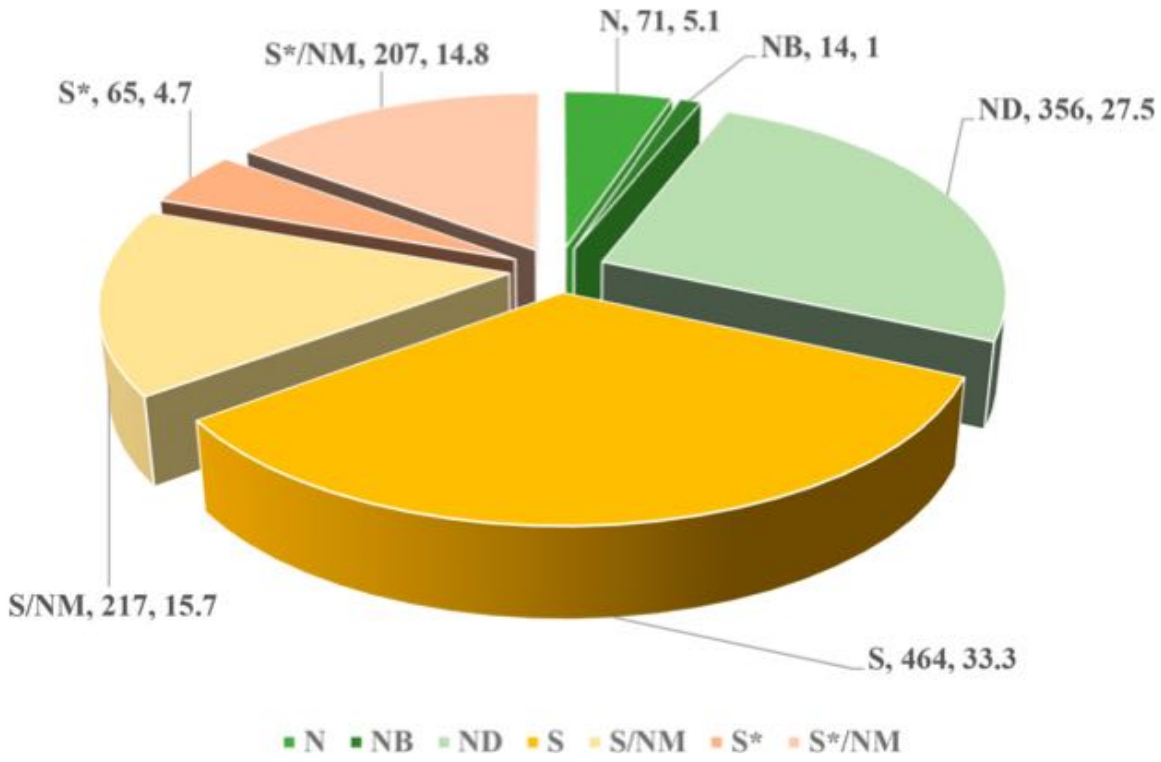


Figure 5. All small-molecule approved drugs 01JAN81 to 30SEP19; n = 1394.

SMALL MOLECULES APPROVED DRUGS

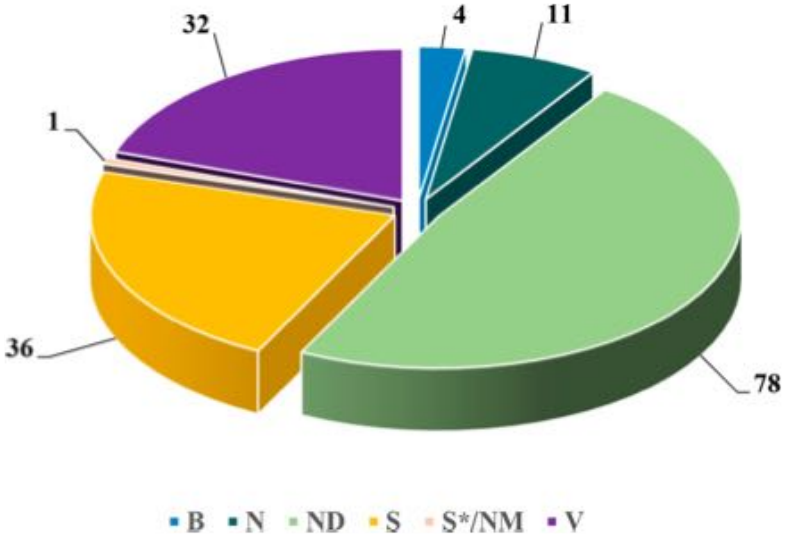


Figure 11. Antibacterial drugs by source.

Figure 12. Antifungal drugs by source.

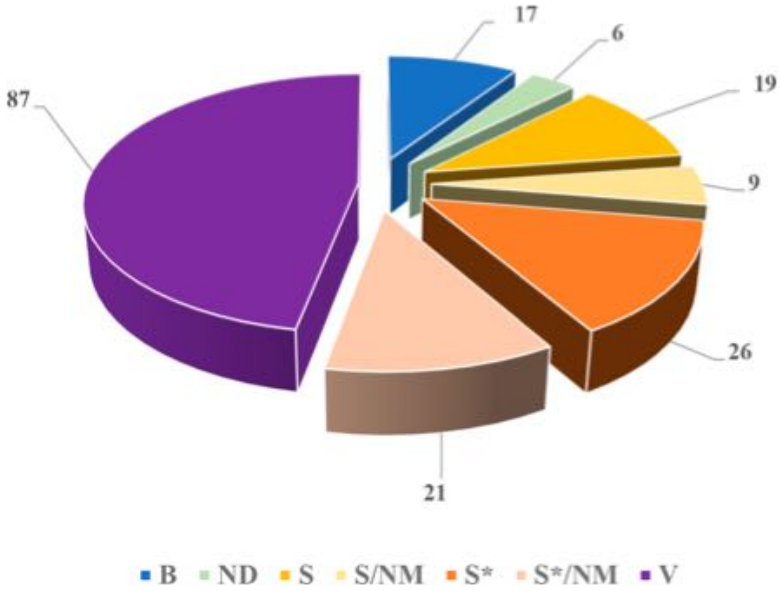


Figure 13. Antiviral Drugs by Source.

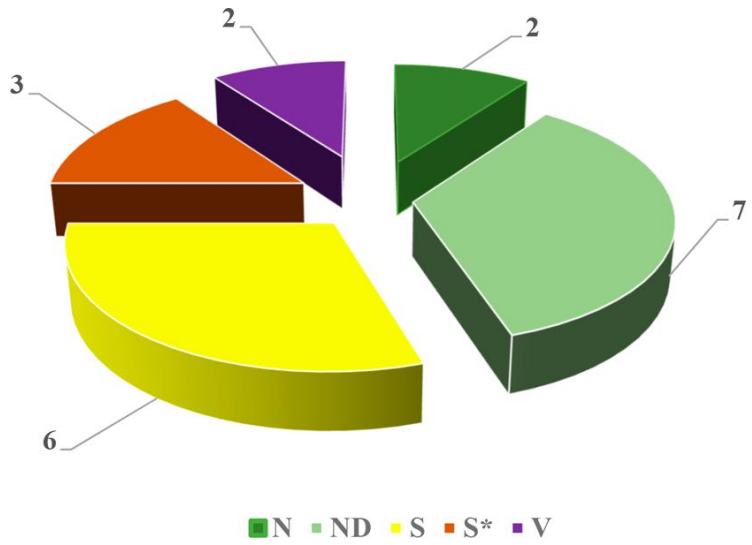


Figure 14. Antiparasitic drugs by source.

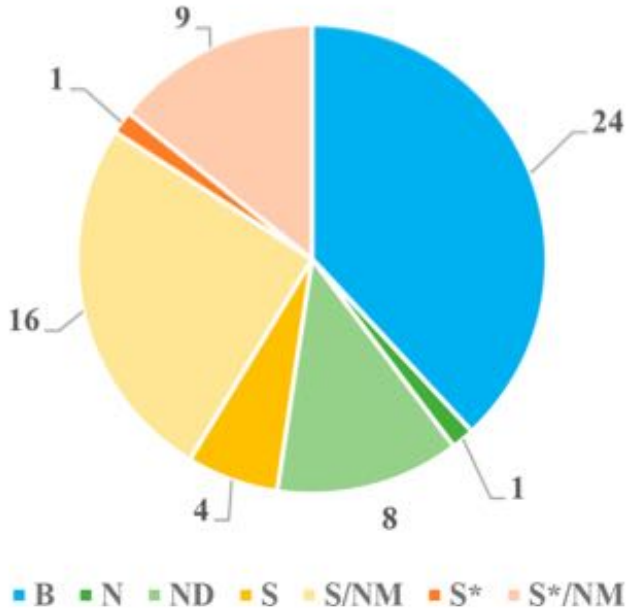


Figure 22. All antidiabetic drugs 01JAN81–30SEP19, n = 63.

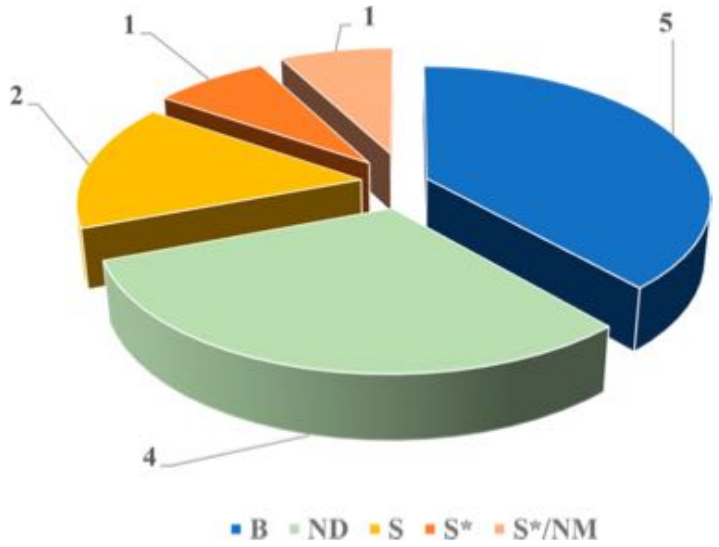


Figure 23. All multiple sclerosis drugs 01JAN81–30SEP19, n = 13.

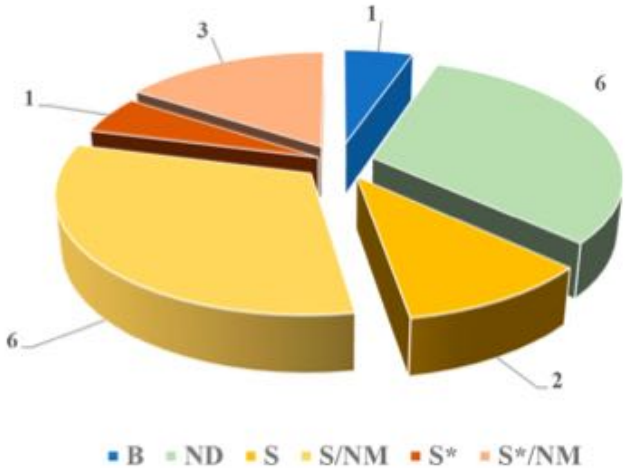


Figure 24. Antiglaucoma drugs 01JAN81–30SEP19, n = 19.

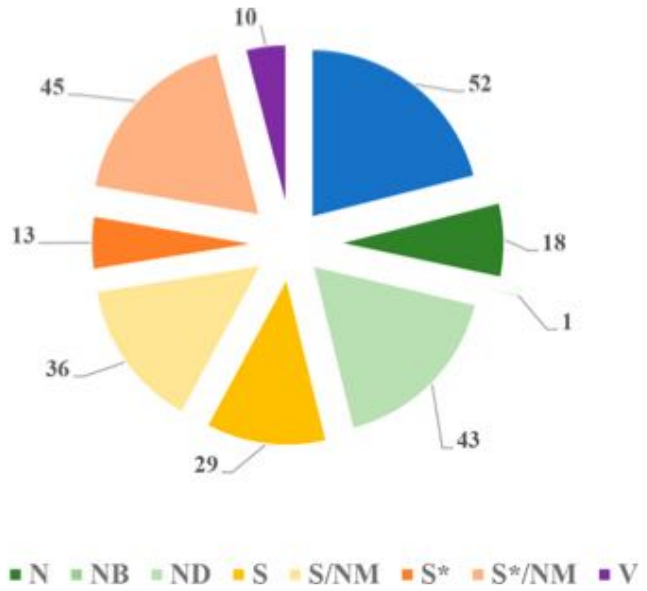


Figure 15. All anticancer drugs 01JAN81–30SEP19, n = 247.

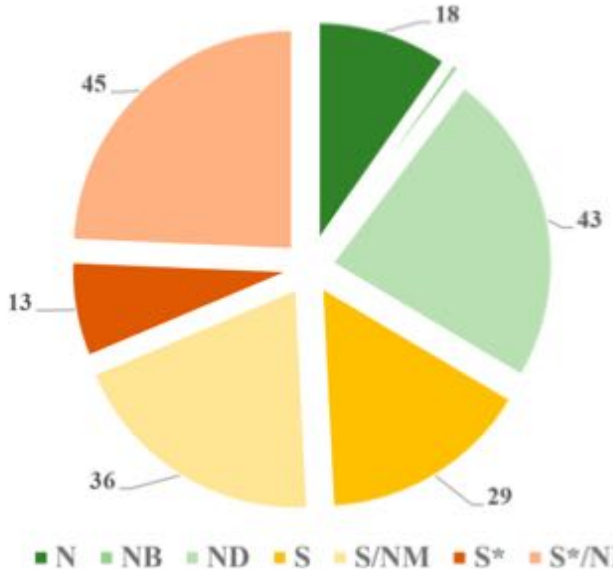


Figure 17. Small anticancer drugs 01JAN81–30SEP19, n = 185.

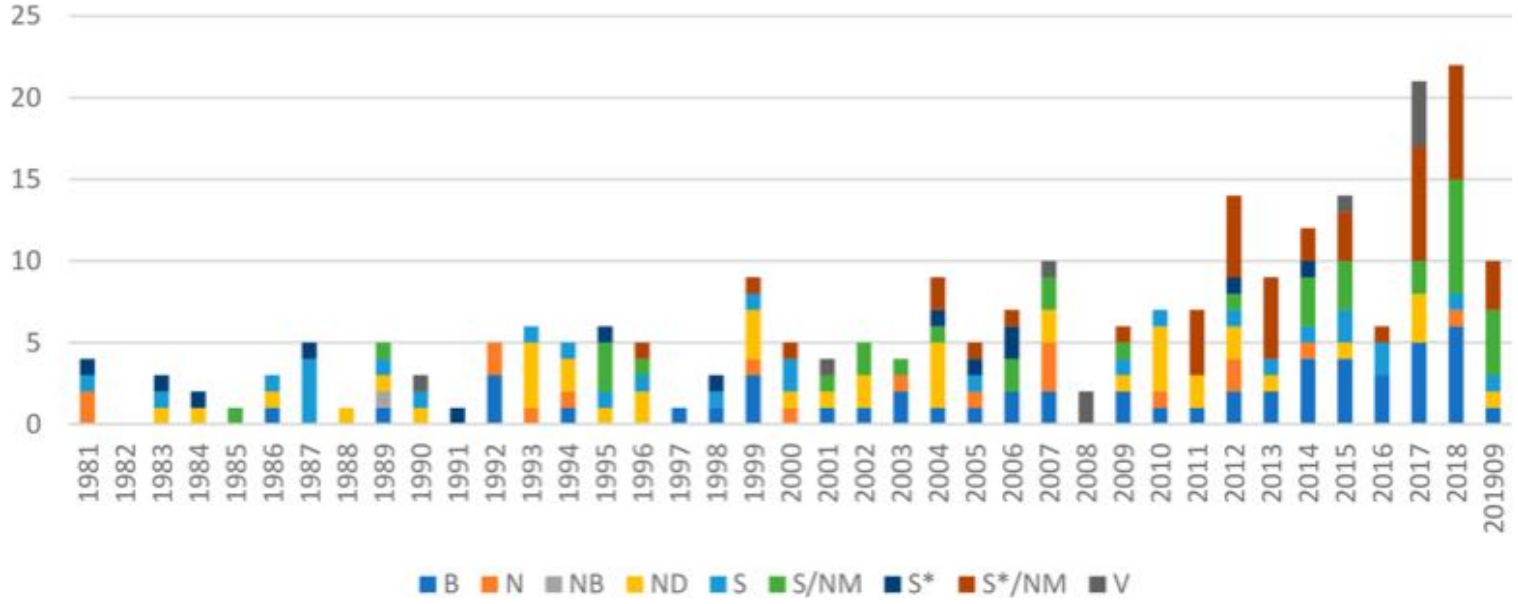


Figure 16. All anticancer drugs 01JAN81–30SEP19, n = 247 (bar chart).

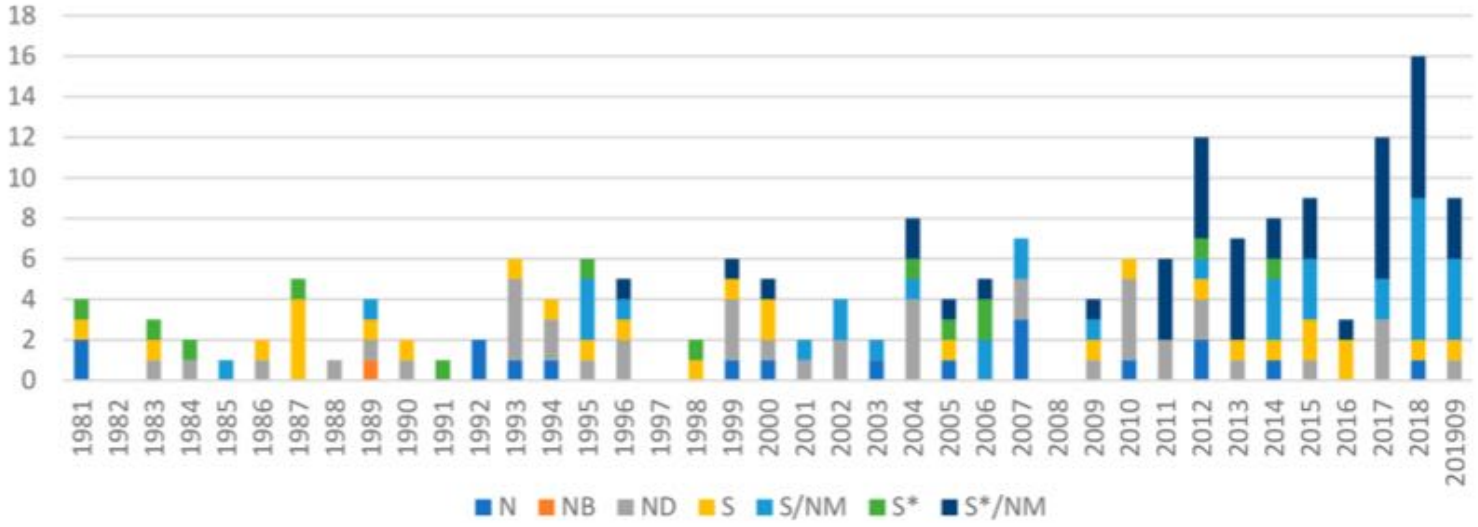


Figure 18. Small anticancer drugs 01JAN81–30SEP19, n = 185 (bar chart).

EMBO reports

viewpoint

Natural products and drug discovery

Can thousands of years of ancient medical knowledge lead us to new and powerful drug combinations in the fight against cancer and dementia?

Hong-Fang Ji, Xue-Juan Li & Hong-Yu Zhang

Throughout our evolution, the importance of natural products for medicine and health has been enormous

…the switch away from natural products to combinatorial chemistry during the 1990s might have led to the current paucity of new drug candidates in the development pipeline…

…the popularity of natural products will continue simply because they are a matchless source of novel drug leads and inspiration for the synthesis of non-natural molecules…

…it remains an important challenge to find biologically active compounds and to develop these into new drugs, even if one uses nature for inspiration

…we need to move beyond either xenohormesis or co-evolution to explain the biological effects of natural products

…natural products provide important clues for identifying and developing synergistic drugs that, so far, research has largely neglected

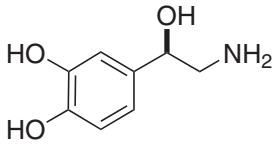
…we have a rich historical record from ancient physicians […], which might provide important clues for developing new drugs…

Lessons from natural molecules

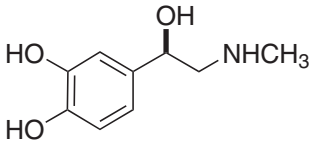
Jon Clardy & Christopher Walsh

Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, USA
(e-mail: jon_clardy@hms.harvard.edu)

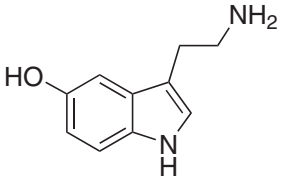
Natural products have inspired chemists and physicians for millennia. Their rich structural diversity and complexity has prompted synthetic chemists to produce them in the laboratory, often with therapeutic applications in mind, and many drugs used today are natural products or natural-product derivatives. Recent years have seen considerable advances in our understanding of natural-product biosynthesis. Coupled with improvements in approaches for natural-product isolation, characterization and synthesis, these could be opening the door to a new era in the investigation of natural products in academia and industry.



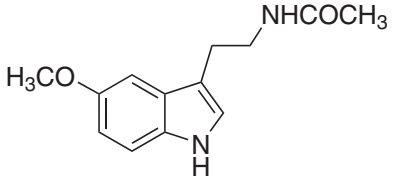
43 Noradrenaline



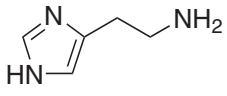
44 Adrenaline



45 Serotonin



46 Melatonin

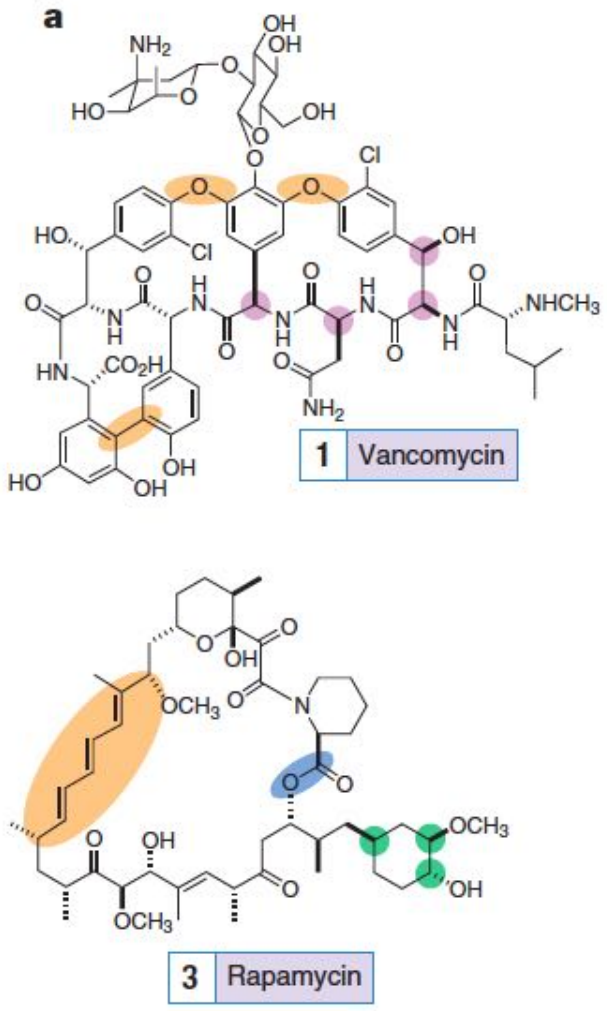


47 Histamine

PROPRIEDADES ESTRUTURAIS:

- Presença de centros estereogênicos e maior complexidade estrutural que as moléculas sintéticas;
- Maior quantidade de relativa de carbono, hidrogênio e oxigênio que as moléculas sintéticas;
- Tamanho (massa molecular > 500Da) e polaridade (maior solubilidade em água).
- Geralmente não seguem a Lei de Lipinski

Clardy & Walsh. Nature, 432: 829.



Lipinski Rule of Five

There are various guidelines to help, the most well-known of which is the

Lipinski Rule of Five

- molecular weight < 500
- logP < 5
- < 5 H-bond donors (sum of NH and OH)
- < 10 H-bond acceptors (sum of N and O)

Note that all numbers are multiples of five, which is the origin of the rule's name.

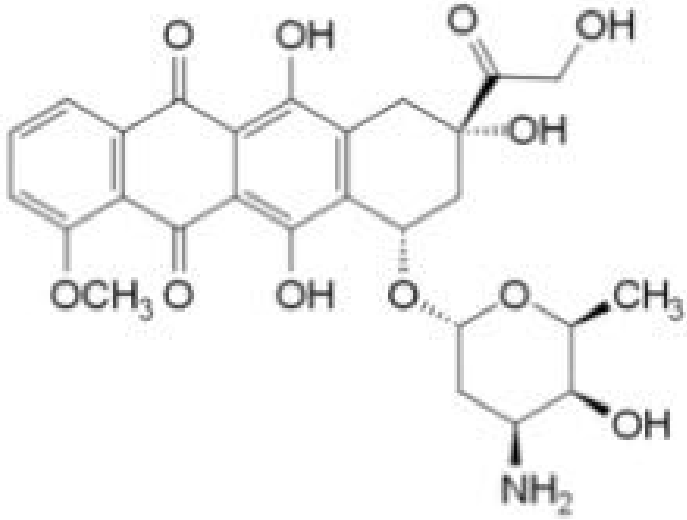
Otherwise absorption and bioavailability are likely to be poor.

NB This is for **oral** drugs only.

DRUG-LIKE PROPERTIES: CONCEPTS, STRUCTURE DESIGN AND METHODS FROM ADME TO TOXICITY OPTIMIZATION. EDWARD H. KERNS

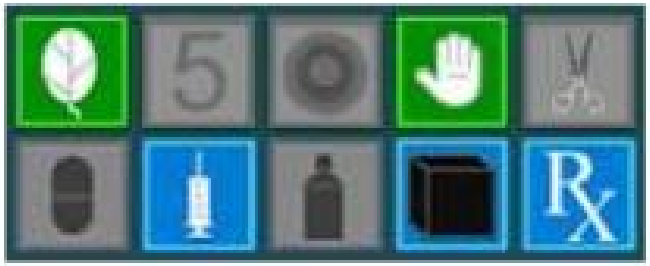
Doxorubicin

bioavailability of approximately 5%.



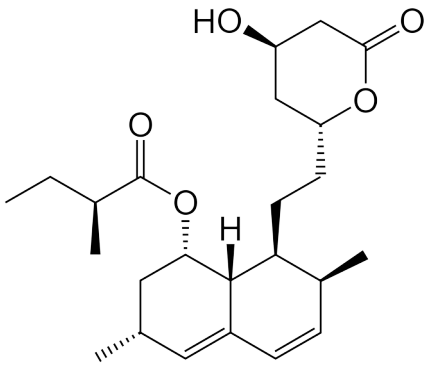
Hydrogen bond donor 7:
Hydrogen bond acceptor 12
Molecular weight 534
Lipophilicity (log P) : -1.7

Guidelines are exceeded for all rules except logP

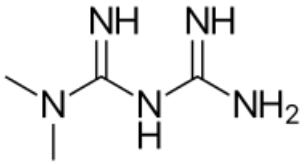


DRUG-LIKE PROPERTIES: CONCEPTS, STRUCTURE DESIGN AND METHODS FROM ADME TOXICITY OPTIMIZATION EDWARD H. KERNS

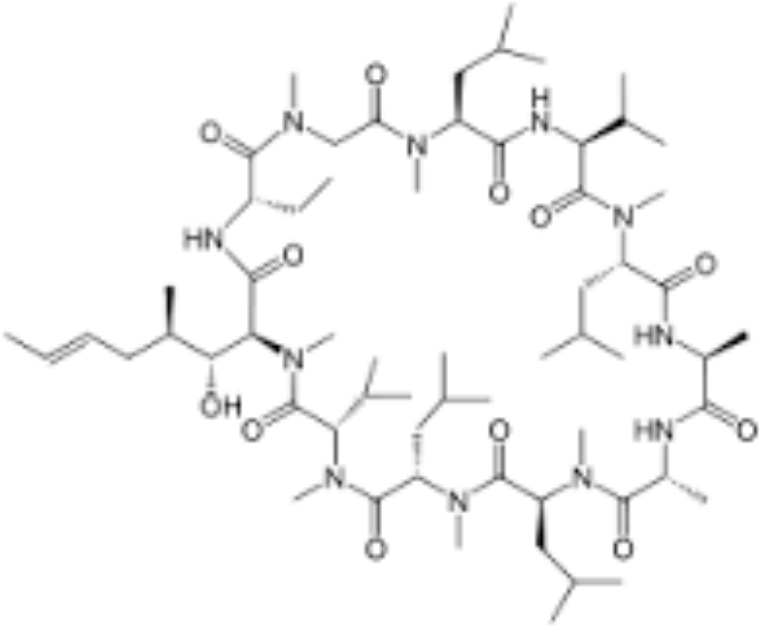
https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL53463



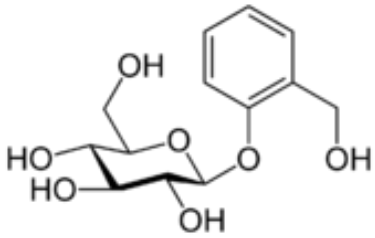
Lovastatina (*Aspergillus terreus*)
Estatina



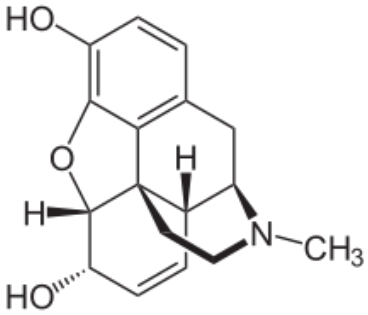
Metformina (*Galega officinalis*)
Hipoglicemiante



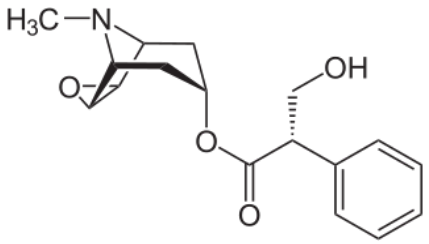
Ciclosporina (*Tolypocladium inflatum*)
Imunossupressor



Salicilina (*Salix* sp.)
AINE



Morfina (*Papaver somniferum*)
Opióide



Escopolamina (*Brugmansia suaveolens*)
Anti-muscarínico

nature chemistry

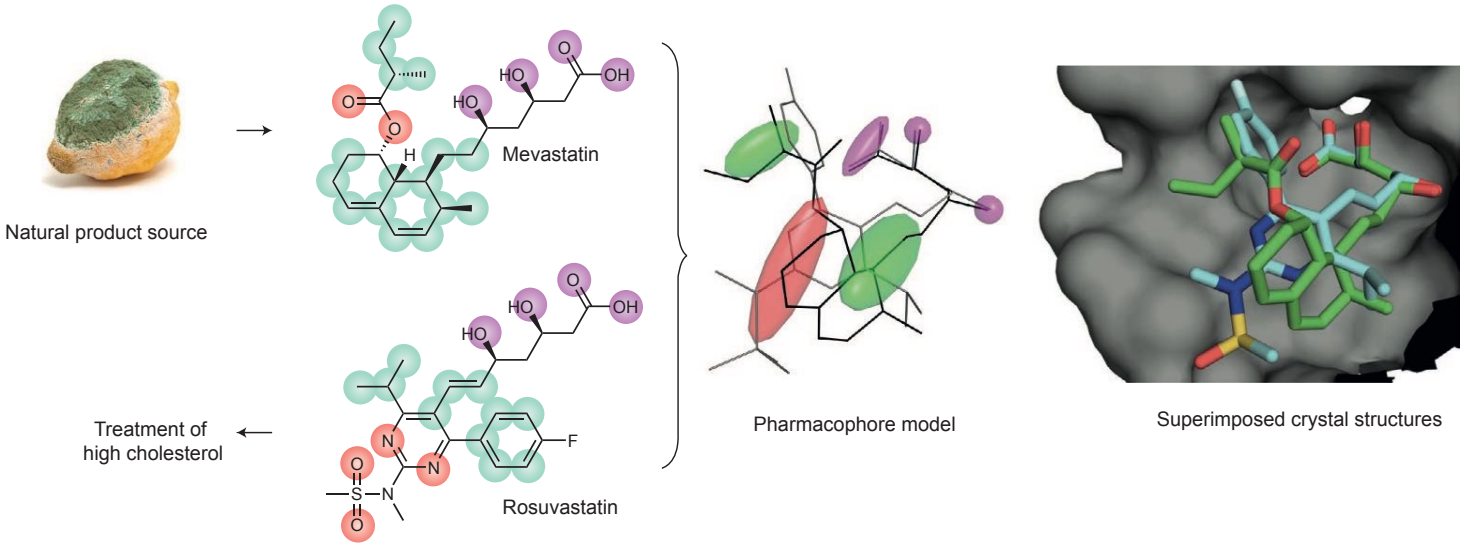
REVIEW ARTICLE

PUBLISHED ONLINE: 25 APRIL 2016 | DOI: 10.1038/NCHEM.2479

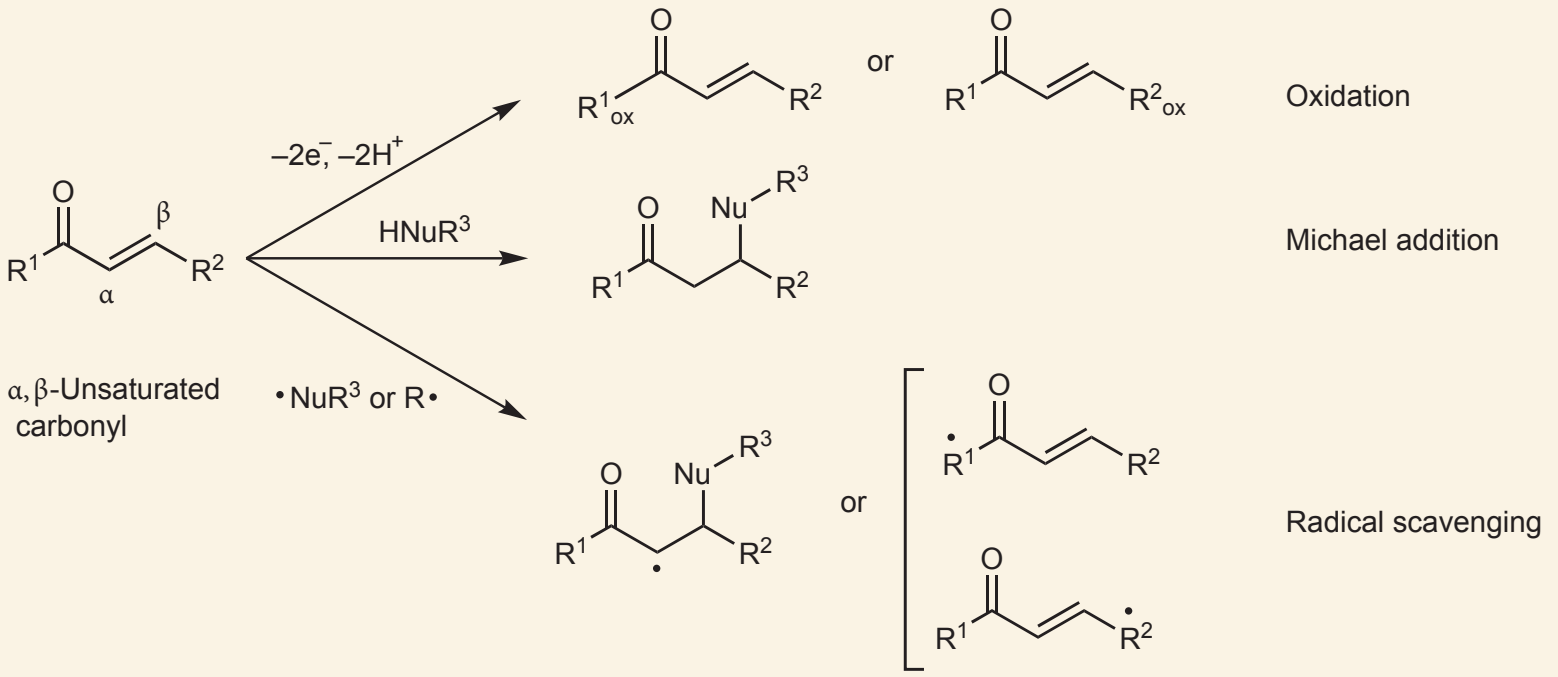
Counting on natural products for drug design

Tiago Rodrigues[1], Daniel Reker[1], Petra Schneider[1,2] and Gisbert Schneider[1]*

Natural products and their molecular frameworks have a long tradition as valuable starting points for medicinal chemistry and drug discovery. Recently, there has been a revitalization of interest in the inclusion of these chemotypes in compound collections for screening and achieving selective target modulation. Here we discuss natural-product-inspired drug discovery with a focus on recent advances in the design of synthetically tractable small molecules that mimic nature's chemistry. We highlight the potential of innovative computational tools in processing structurally complex natural products to predict their macromolecular targets and attempt to forecast the role that natural-product-derived fragments and fragment-like natural products will play in next-generation drug discovery.



Box 1 | Natural products containing α,β-unsaturated carbonyls — a liability for drug design?



The Nobel Prize in Physiology or Medicine 2015

Ill. N. Elmehed. © Nobel Media AB 2015.

William C. Campbell

Prize share: 1/4

Ill. N. Elmehed. © Nobel Media AB 2015.

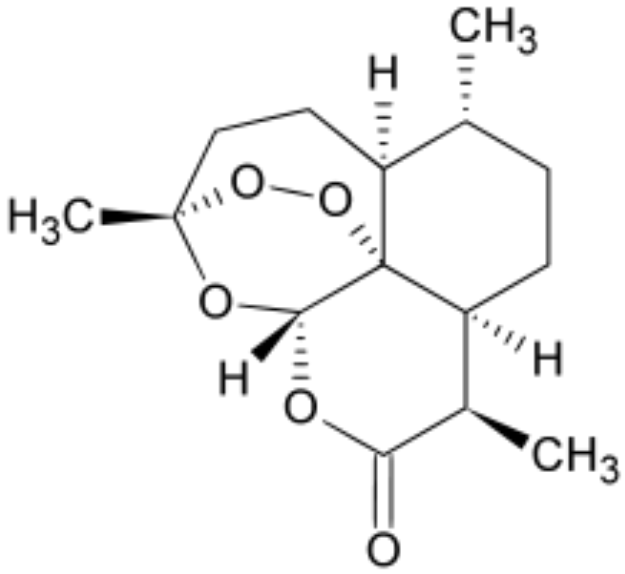
Satoshi Ōmura

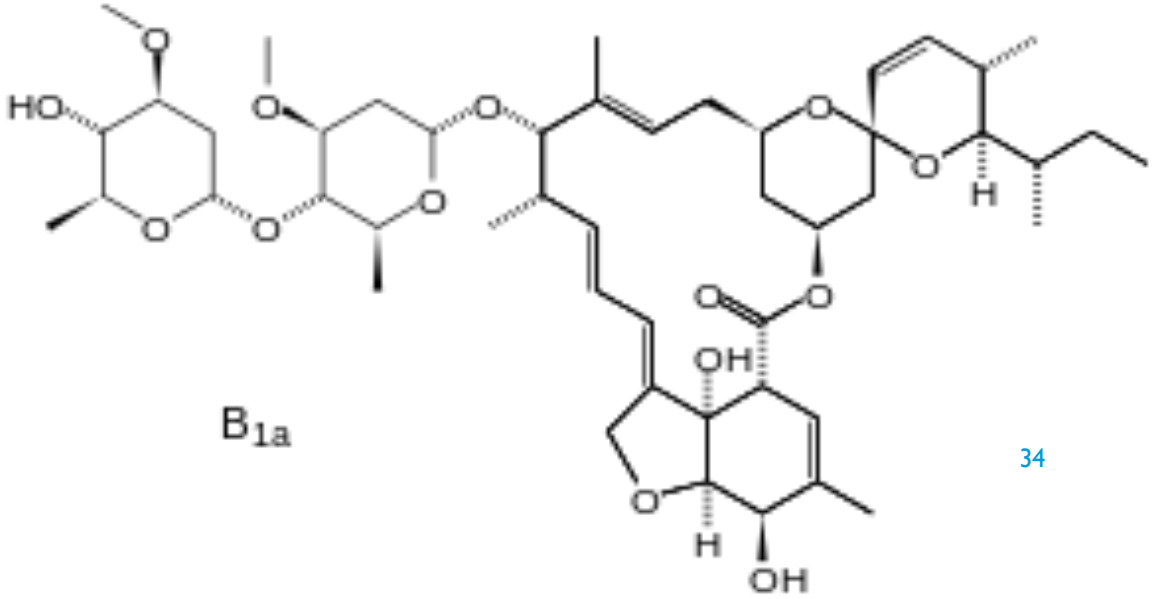
Prize share: 1/4

Ill. N. Elmehed. © Nobel Media AB 2015.

Youyou Tu

Prize share: 1/2





B_{1a}

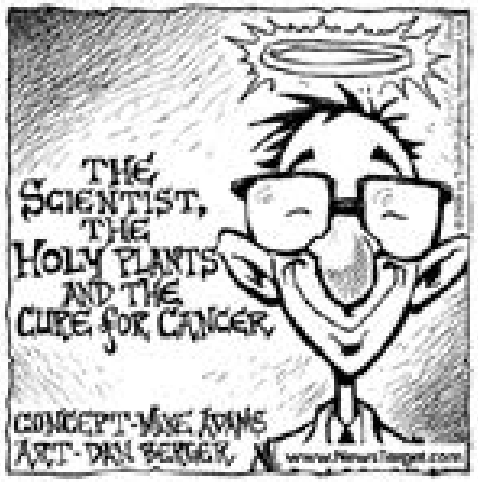
LIMITAÇÕES

- Suprimento para garantir avanços do processo de P&D do medicamento
  - Extrativismo
  - Cultivo do organismo produtor
  - Síntese em laboratório
- Dificuldade de modificação estrutural – “domesticação” da molécula
- Toxicidade

DESAFIOS:

- Redução da toxicidade do tratamento
- Resistência a múltiplas drogas
- Novas moléculas
- Novos alvos
- Atrelar a descoberta de moléculas com novos alvos terapêuticos

PONTOS PARA REFLEXÃO:

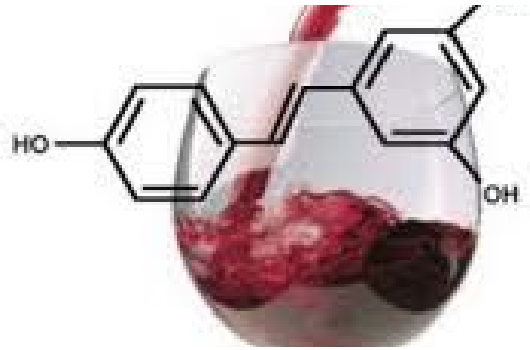


- 80% da população mundial faz uso de medicamentos alternativos (baseados em preparações de plantas) no tratamento de doenças (WHO)
- Estima-se um mercado de 18 bilhões de dólares
- Crença em efeitos colaterais menores
- Conhecimento tradicional associado

PONTOS PARA REFLEXÃO:

- Poucos dados em relação a pureza, segurança e eficácia das medicações “alternativas”
  - Por exemplo – preparações de gingeng são padronizadas a partir do % de ginsenosídoes, mas existem 30 compostos diferentes dessa classe que podem contribuir com relação a atividade biológica
- Falta de testes clínicos padronizados
- Desconhecimento dos efeitos colaterias
- Interações medicamentosas
- Preconceito (?)

RESVERATROL

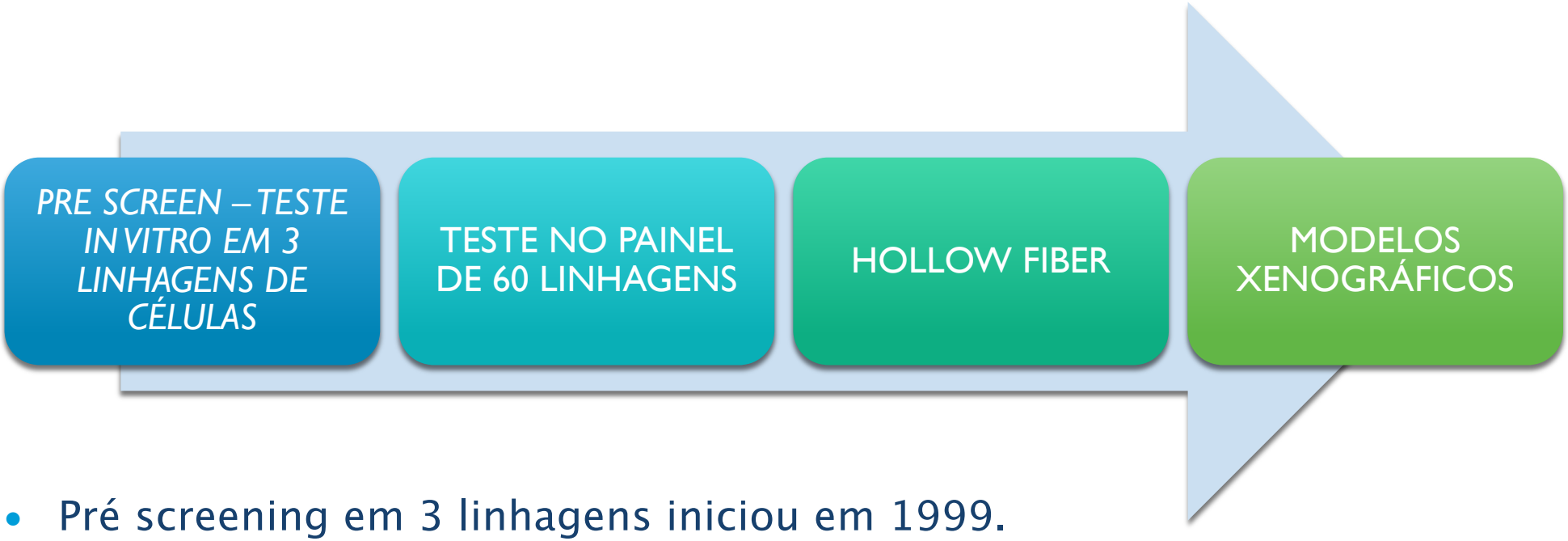


- Efeitos do resveratrol em modelos animais – dose efetiva (20 mg/kg)
- Concentração de resveratrol numa garrafa de vinho tinto (2 mg/L)
- “Dose efetiva” de vinho para um indivíduo de 70 kg – 700 garrafas de vinho por dia

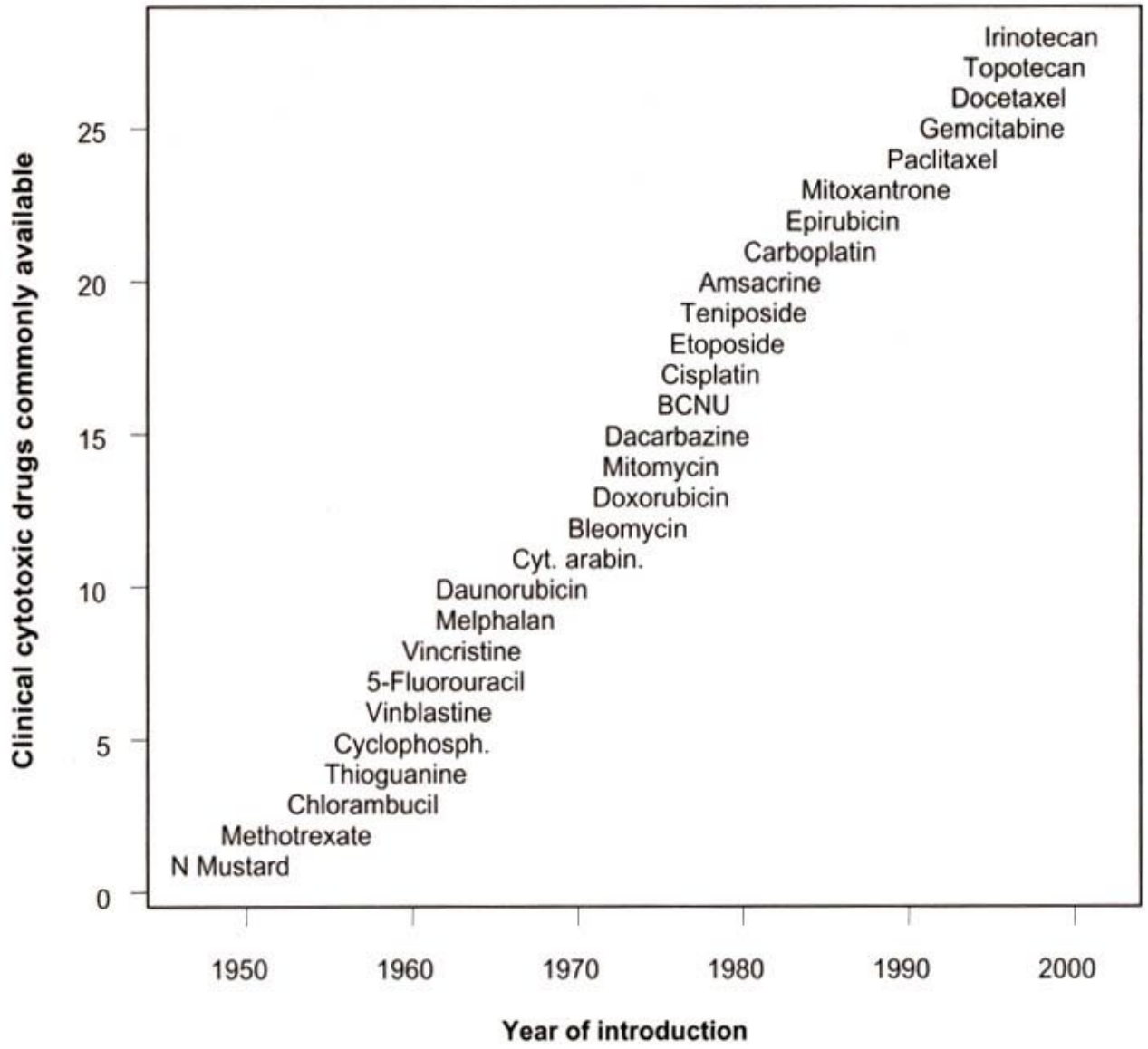
PESQUISA DE PRODUTOS NATURAIS COM ATIVIDADE ANTICÂNCER – HISTÓRICO:

- Iniciou em 1955 no Instituto Nacional do Câncer (EUA) através de *Screening*
- Acima de 400 000 compostos foram testados
- Posteriormente passou a englobar micróbios e organismos marinhos
- Em 1980 foi interrompido em função dos poucos compostos identificados com o uso das linhagens leucêmicas de camundongos (L1210 e P388)

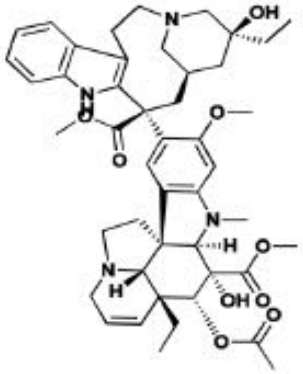
PESQUISA DE NOVOS FÁRMACOS ANTI-CÂNCER:



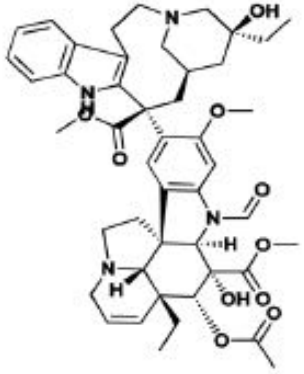
- Pré screening em 3 linhagens iniciou em 1999.
- Em seguida em 60 linhagens- Elimina 80% dos candidatos.
- Identificação o alvo molecular antes de proceder o teste xenografico , *in vivo*- desde de 1998.
- Tumores sólidos



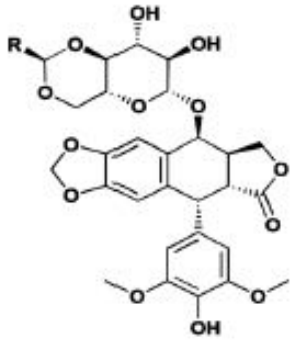
70% dos quimioterápicos tem sua estrutura baseada num produto natural!!!



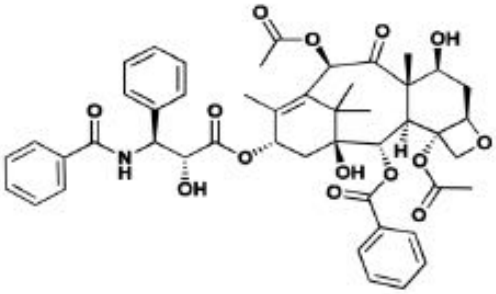
Vinblastine



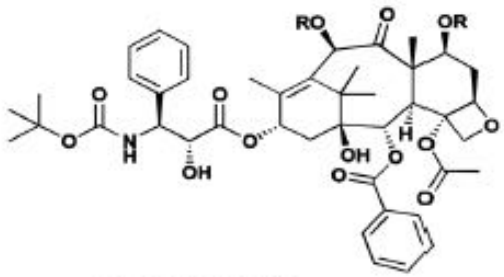
Vincristine



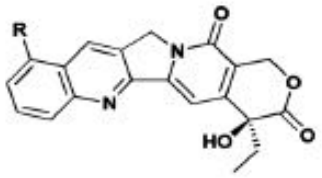
Etoposide, R = CH_3
Teniposide, R = a-thiazole



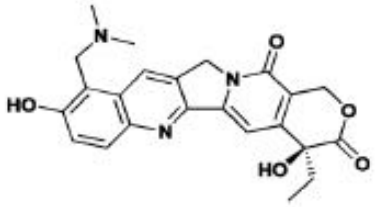
Paclitaxel



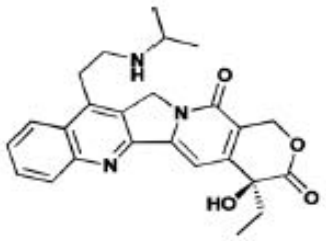
Taxotere, R = H
Cabzitaxel, R = CH_3



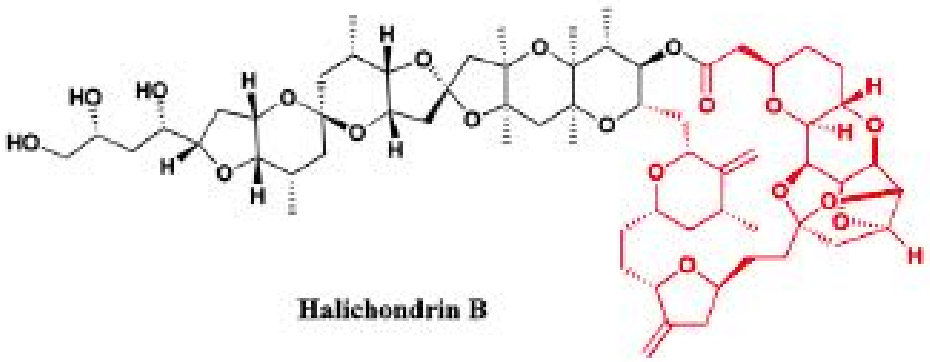
Camptothecin, R = H
9-Aminocamptothecin, R = NH2
9-Notrocamptothecin, R = NO2



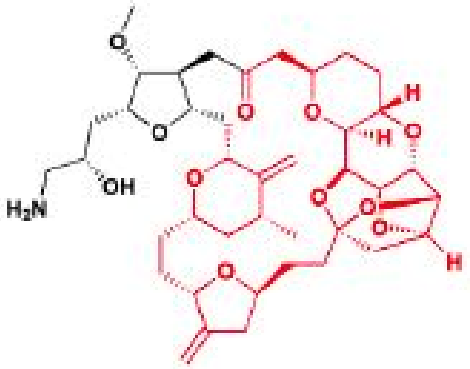
Irinotecan



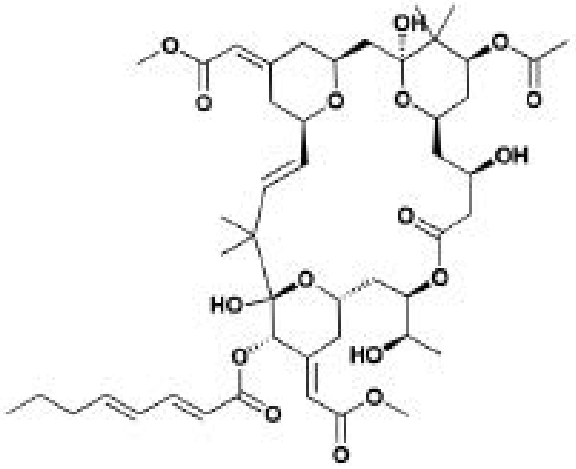
Belotecan



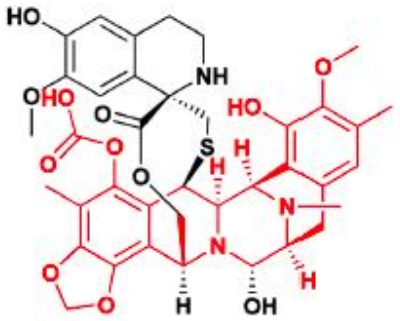
Halichondrin B



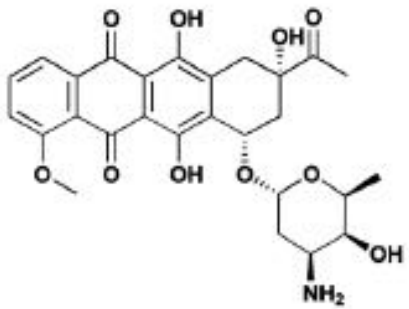
E_{7389} (Eribulin)



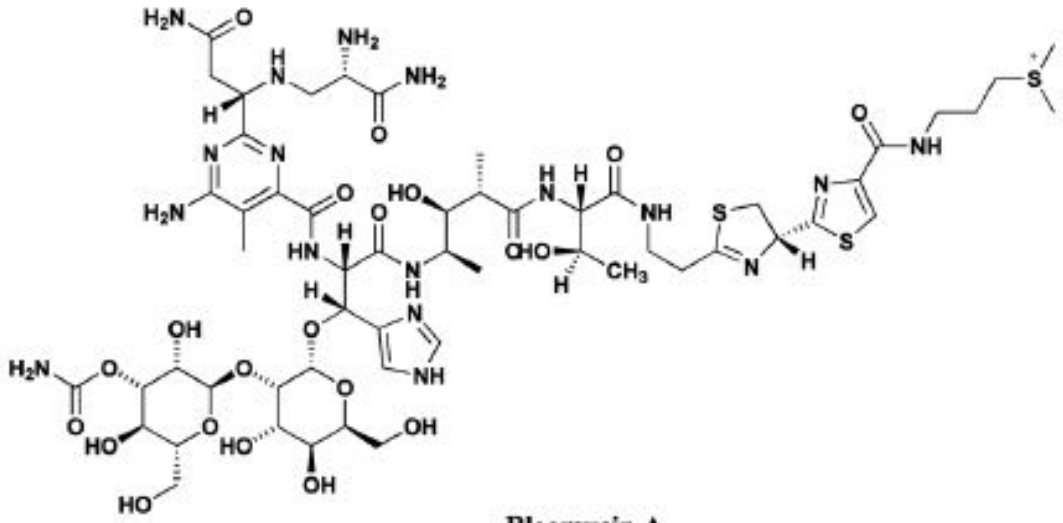
Bryostatin 1



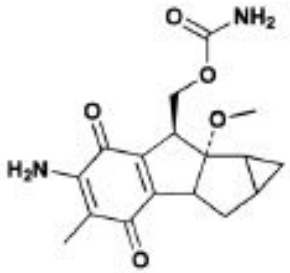
Ecteinascidin 743 (Yondelis™)



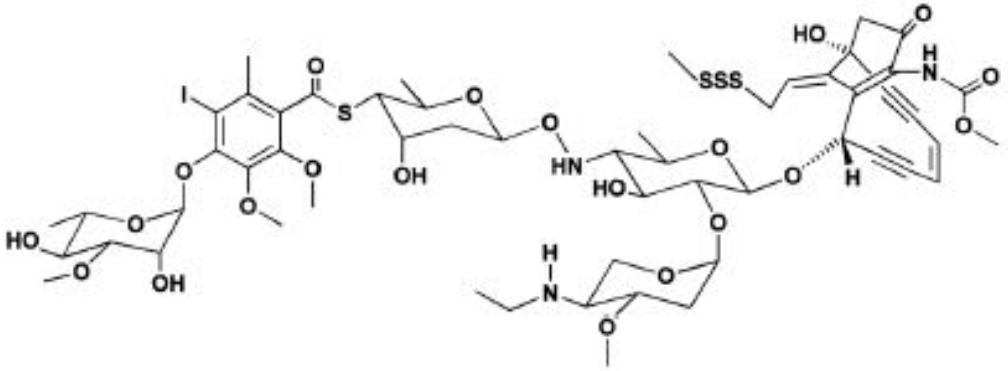
Daunomycin



Bleomycin A_2

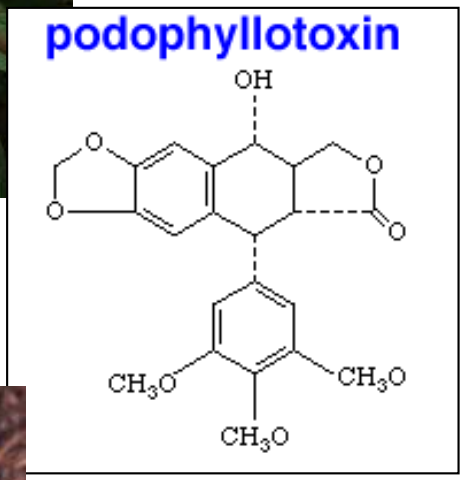


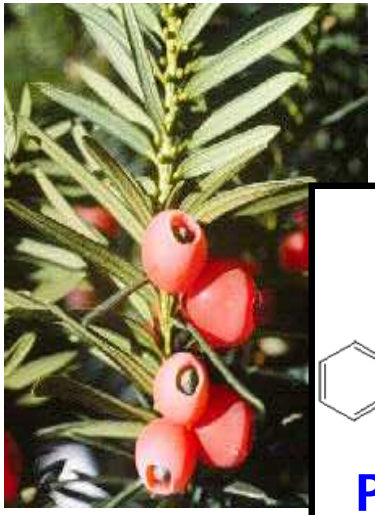
Mitomycin C



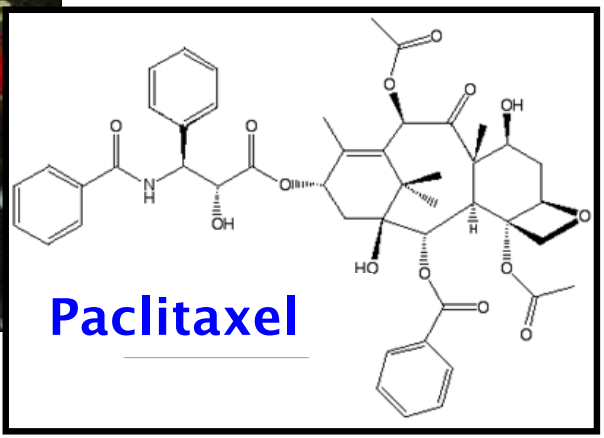
Calicheamicin-γI_1

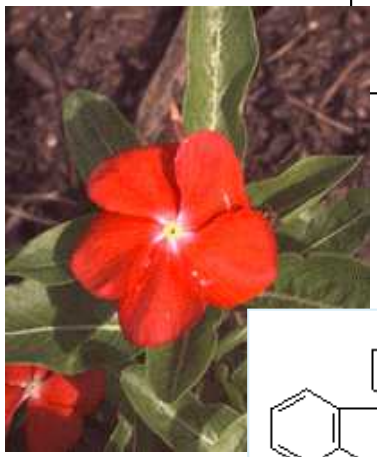
podophyllotoxin



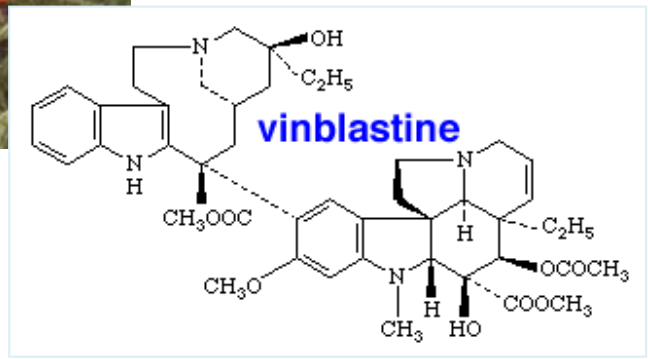


Paclitaxel

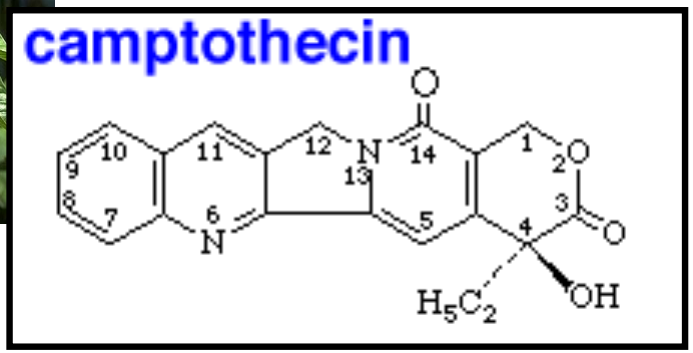




vinblastine



camptothecin



ALCALOÍDES DA VINCA

Catharanthus roseus

USO POPULAR:

Europa: tratamento da diabetes.

Índia: picada de inseto.

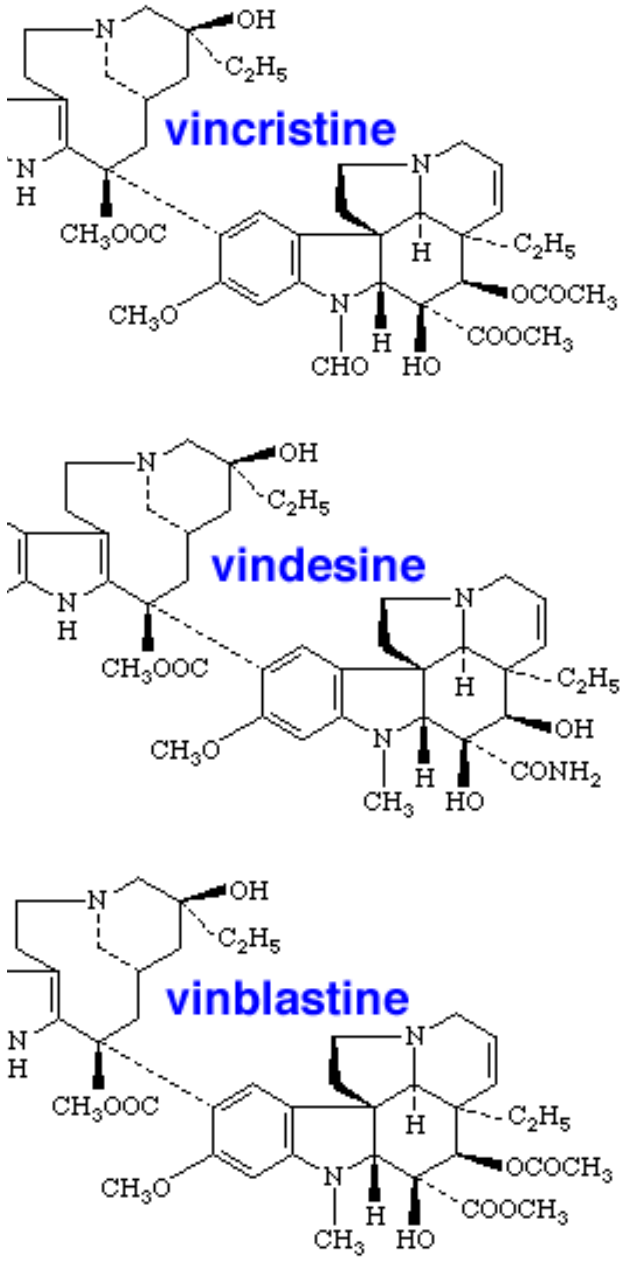
Hawai: hemorragia.

América central e do sul: congestão nasal e inflamação.

Caribe: irritação e infecção.

ALCALÓIDES DA VINCA

- Originalmente isolados em 1958 por Robert Noble e Charles Thomas Berr no Canadá
- Ely Lilly identificou a citotoxicidade em 1959
- Rendimento 0.00002%
- Mecanismo de ação: inibição da polimerização da tubulina
- Aprovação para uso clínico em 1963

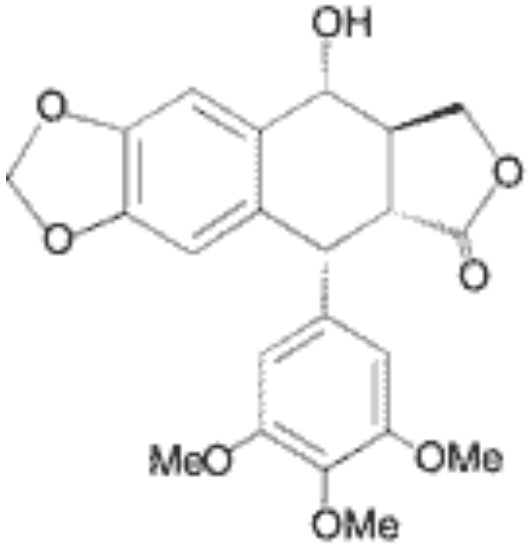


ALCALOÍDES DA VINCA

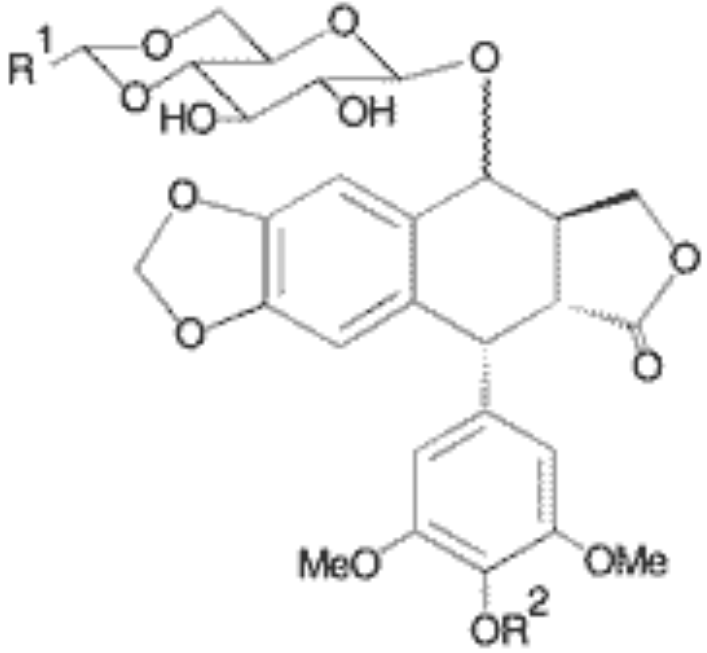
- Uso clínico:
  - Vincristina – Oncovin®, Leucemia, tumor de wilms e linfoma
  - Vinblastina - Velban®, Linfoma de Hodgkin
- Efeitos adversos:
  - Mielossupressão (branda), parestesias
  - Alopecia

Podophyllum spp. -BERBERIDACEAE

Podofilina (lignano) verruga genital
Berberine (alcaloíde) febre e infeção
Podofilotoxina (derivado da podofilina) câncer

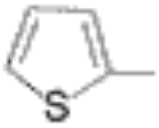


podophyllotoxin



etoposide R^1 = Me, R^2 = H,

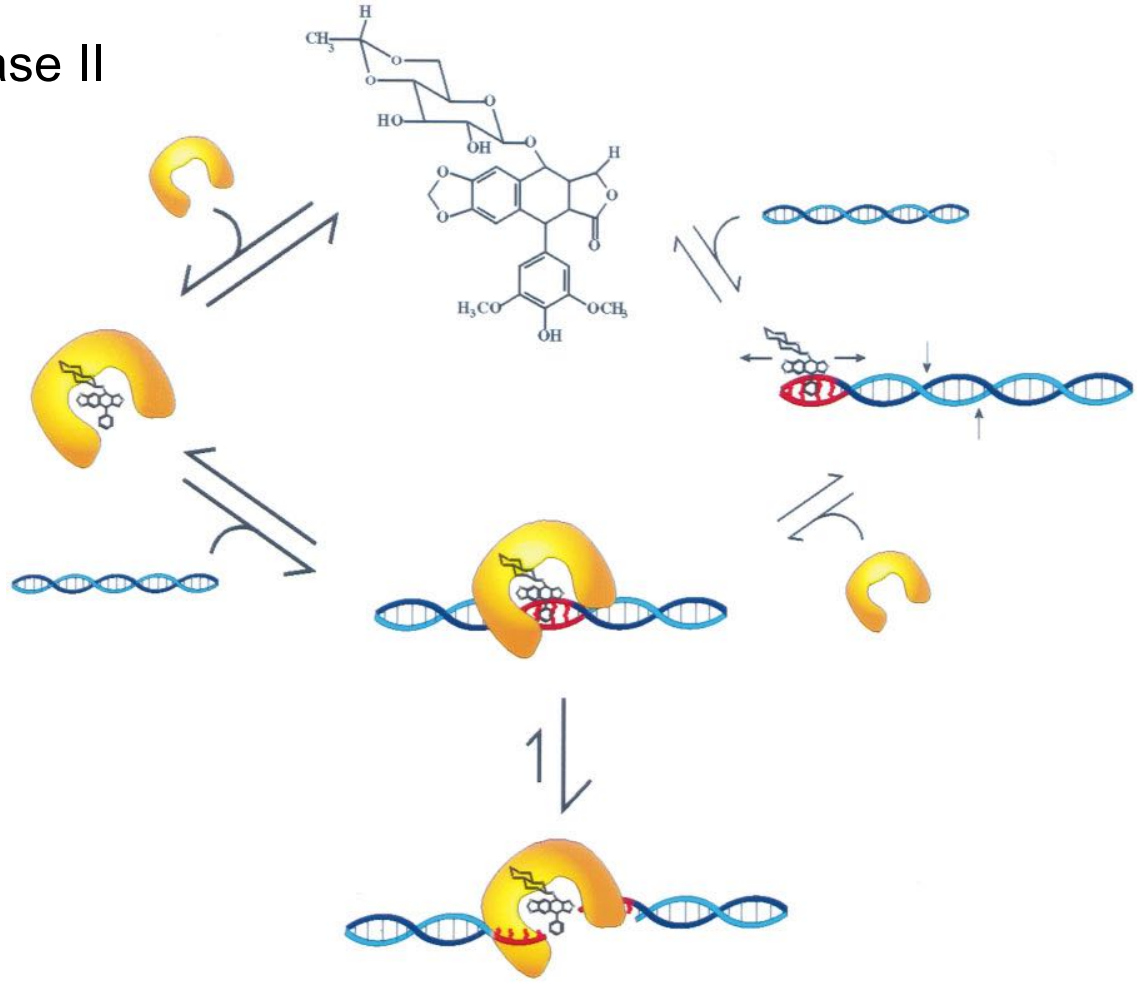
etopophos R^1 = Me, R^2 = $PO(OH)_2$,

teniposide R^1 =  , R^2 = H,

CPH 82 R^1 =  , R^2 = H

MECANISMO DE AÇÃO

Inibição da topoisomerase II

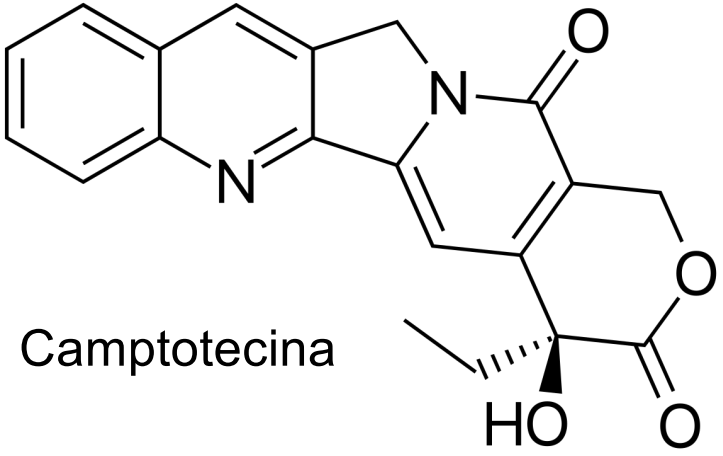


AÇÃO TERPÊUTICA DO ETOPOSIDE (VEPESID®) E TENOPOSIDE (VUMON®)

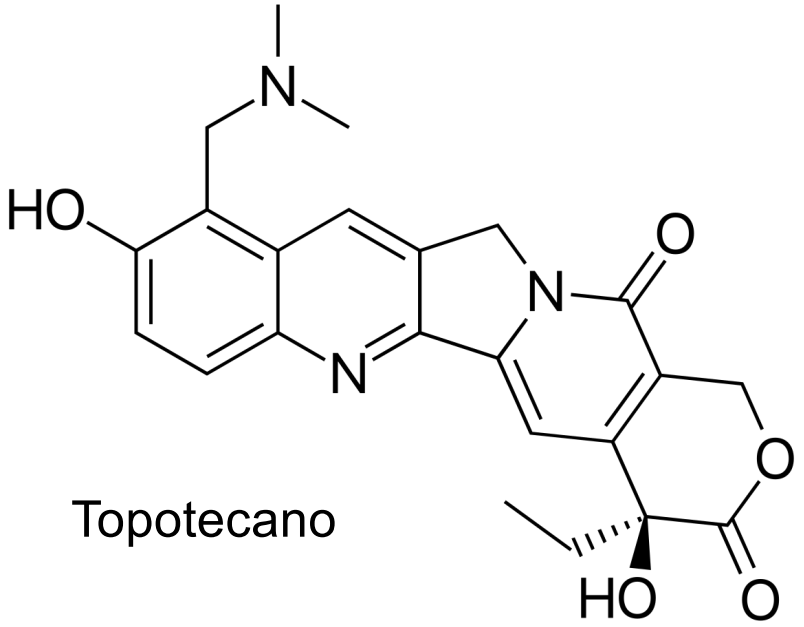
- Usada em vários tipos de cânceres
  - Cancer de testículo – não responde a outro tratamento.
  - Primeira escolha no câncer de pequenas células de pulmão.
  - Saroma de Kaposi, linfomas e melanomas malignos.

Camptotheca acuminata (CHINA E TIBET)

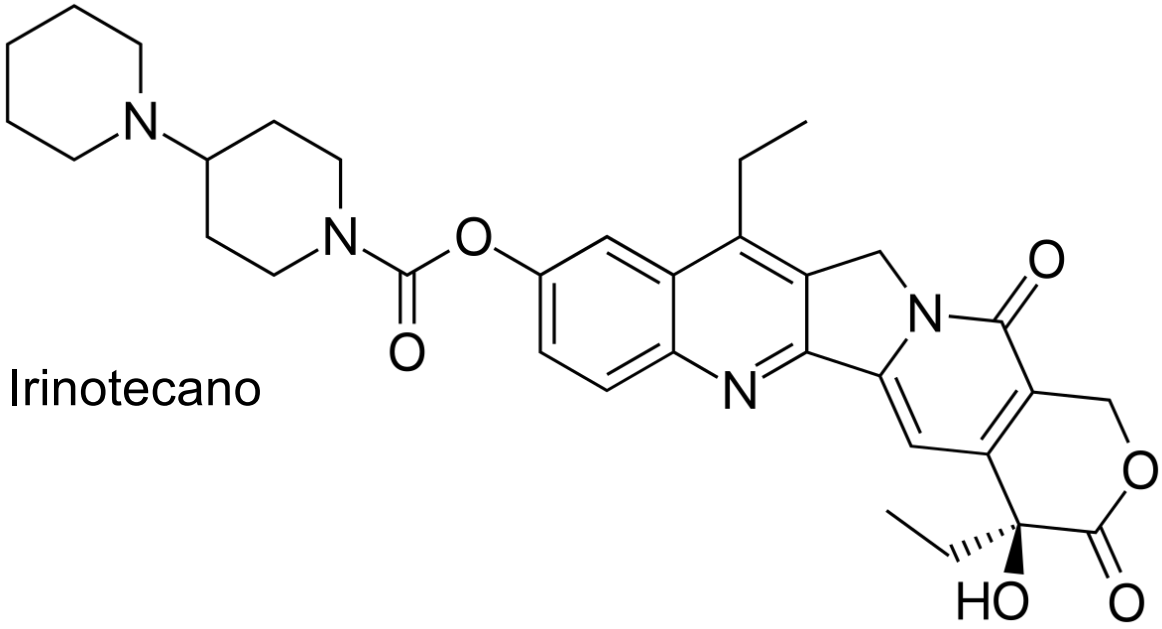
- 1950 screening no NCI
- 1966 Isolado um alcalóide da casca (quinolina)
- Estudos em tumores experimentais confirmam a atividade anticâncer.



Camptotecina

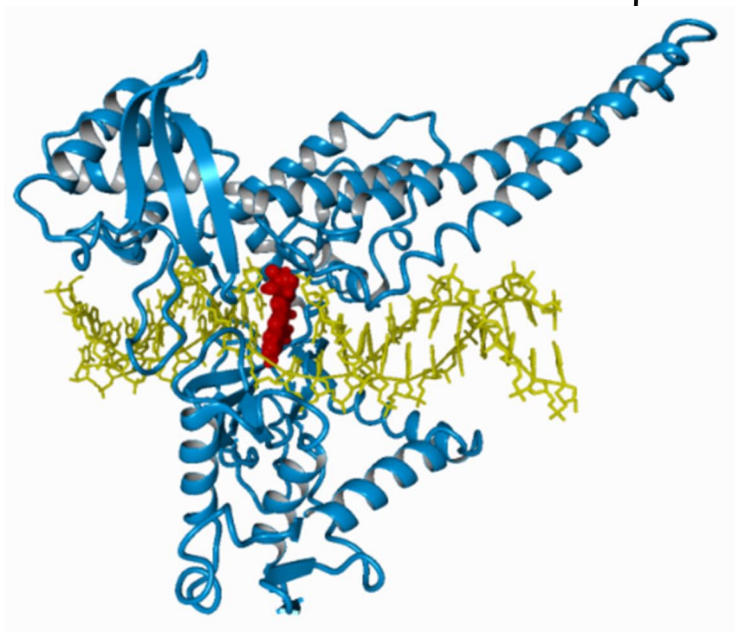


Topotecano



Irinotecano

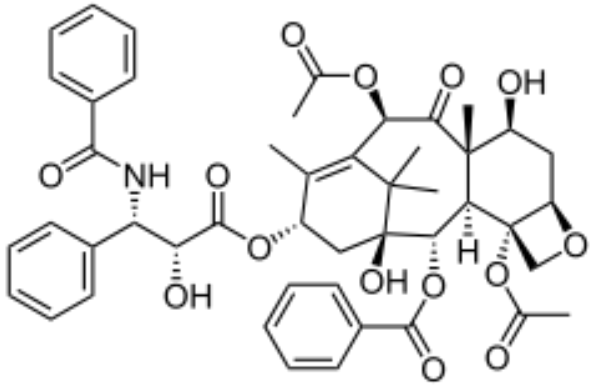
MECANISMO DE AÇÃO



DESENVOLVIMENTO

- O Topotecan foi aprovado pelo FDA em 1996 para o tratamento do câncer de ovário resistente a outros quimioterápicos.
  - Produzido pelo Glaxo Smith Kline (GSK) com o nome comercial de Hycamtin®
- O Irinotecan (camptosar ®) foi aprovado pelo FDA em 1996 para tratamento do câncer coloretal resistente a outros fármacos.
  - Produzido Pharmacia & Upjohn
- O Rubitecan® (9 amino camptotecina) encontra-se em estudo clínico no câncer de pâncreas.
- Outros derivados estão sendo sintetizados para uso em outros tipos de câncer e atividade antiviral.
- As plantações de *C. acuminata* nos EUA produziram baixos níveis de Camptotecina.
- Buscou-se então a opção de novas espécies *(Camptoteca lowreyana)*

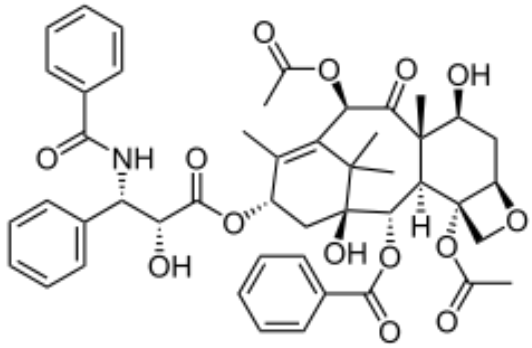
PACLITAXEL:



- *Taxus brevifolia* – coletada no estado de Washington USA em 1962 – Botânico Arthur S. Barclay.
- Jonathan Hartwell – NCI-USA – Extrato com potente atividade em leucemia murina e células KB.
- Isolamento do taxol – 1964.
- Elucidação estrutural – 1971 – Wani et al.

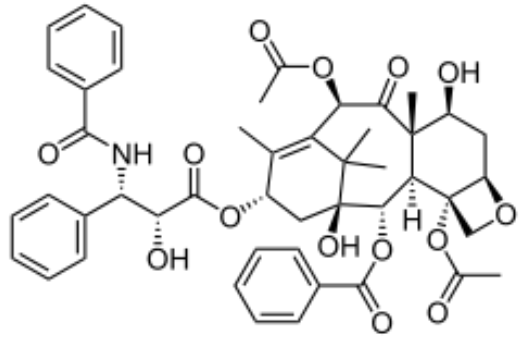
Wani & Horwitz, 2014. Anti-cancer Drugs 25: 482.

PACLITAXEL:



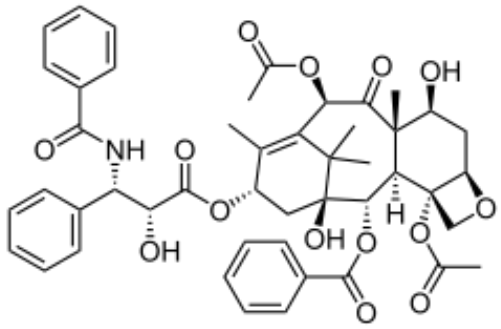
- Mecanismo de ação – 1977 – Susan Band Horwitz
- Estudos em HeLa
  - Bloqueio em metafase
  - Aumento da polimerização e estabilização da tubulina
  - Diferente dos alcalóides da vinca
- 1979 – primeiro paper do MoA é publicado

PACLITAXEL:



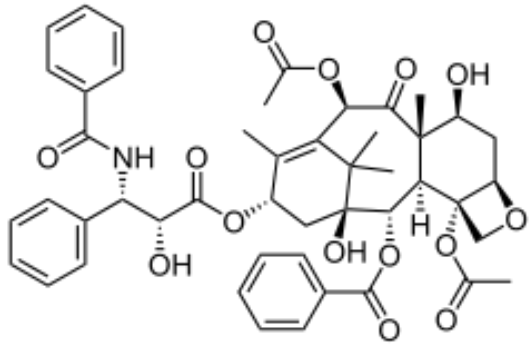
- Estudos pré-clínicos:
  - Ativo em 13/14 tumores murinos transplantáveis
  - Remissão completa em alguns casos
  - Ativo em 15/16 tumores xenográficos
  - Estudos de toxicologia pré-clínica
    - Testes em ratos, camundongos e cães
    - Principais efeitos: hematopoiéticos, gastrointestinais e neuromotores
    - Cães foram mais sensíveis

PACLITAXEL:



- Suprimento da molécula:
  - O estudo clínico foi lento em função da pouca disponibilidade da substância.
  - Rendimento: 1 árvore e meia para cada grama de taxol (árvores de 100 anos).
  - Tratamento usual: 2g/paciente
  - 40.000 mulheres morriam por ano de câncer de mama.
  - Bristol Myers Squibb investiu na plantação de mais 100 milhões de árvores.
  - Em 1991/92 , quilos de Taxol foram produzidos a partir da casca da árvore (semi-síntese).

PACLITAXEL



- Testes clínicos:
  - Baixa solubilidade atrasou entrada em testes clínicos
  - 1a tentativa em 1983 - primeiro paciente que recebeu taxol morreu de choque anafilático
  - 1983 -1988: Trabalhos na formulação, forma de administração e hipersensibilidade
  - Solução: pré-tratamento com anti-histamínicos e glicocorticóides.
  - Administração por infusão durante 24 horas
  - Viabilização dos testes clínicos
  - 29 de dezembro de 1992 – aprovação do FDA

Advanced Drug Delivery Reviews 122 (2017) 20–30

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

The battle of "nano" paclitaxel

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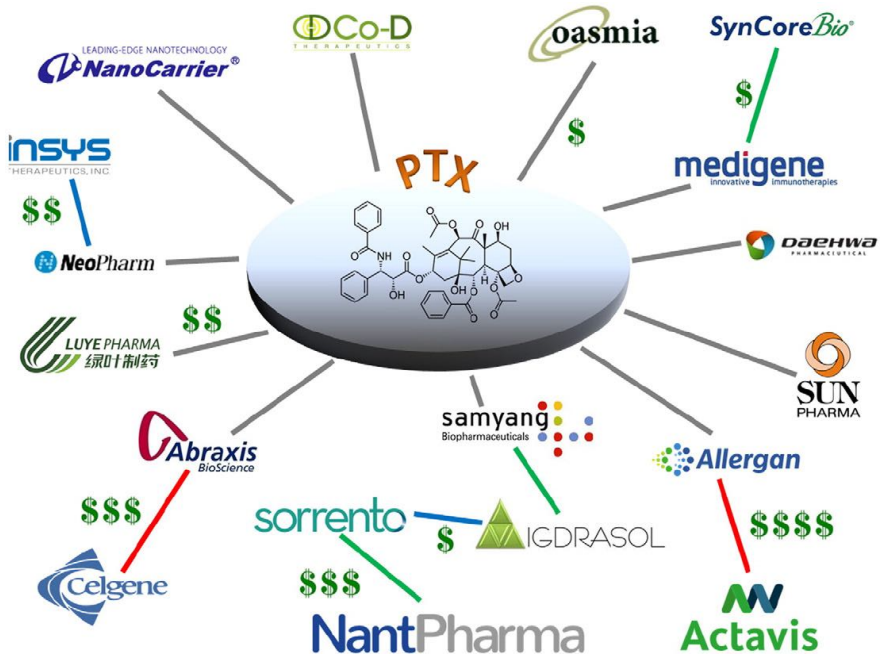
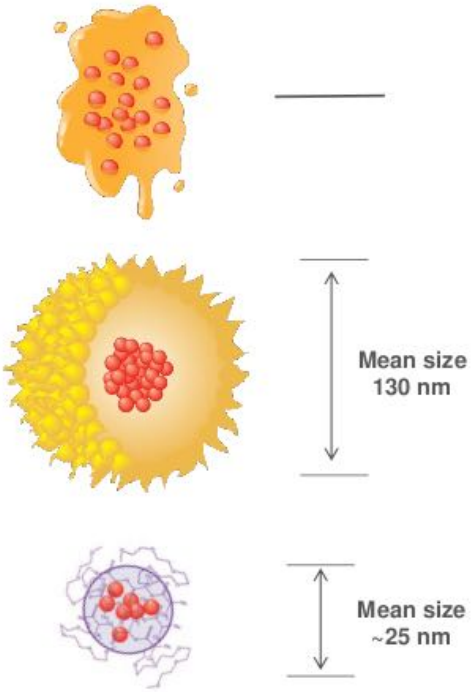


Generation		Formulation	Maximum Tolerated Dose	Peak Product Sales
1st	**Taxol®** paclitaxel	**Cremophor EL** excipient: Polyoxyethylated castor oil	**175 mg/m²**	~ $1.6B (WW in 2000)
2nd	***Albumin-bound* paclitaxel**	**Biological** polymer: Donor-derived human serum albumin (HSA)	**260 mg/m²**	$ 2.2 B* (2020) MBC, NSCLC, PC
3rd	**Cynviloq** paclitaxel polymeric micelle	**Chemical** polymer: Poly-lactide and polyethylene glycol diblock copolymer	**>300 mg/m²** **(up to 435 mg/m²)**	Conversion of paclitaxel sales + new indications



*Celgene Presentation at JPM Healthcare Conference Jan 2015

COUNTERTHINK

WHAT WILL NEVER HAPPEN

WHAT WOULD REALLY HAPPEN