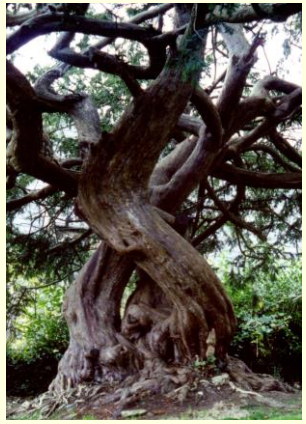
Natural Product-Derived Drugs

The Wonder Drugs That Do Not Follow Medicinal Chemistry Dogma

Plants (leaves, bark and roots) can contain up to 40,000 unique natural products



**"If you can look into seeds of time
And say which grain will grow and
which will not; Speak to me then"
Macbeth**

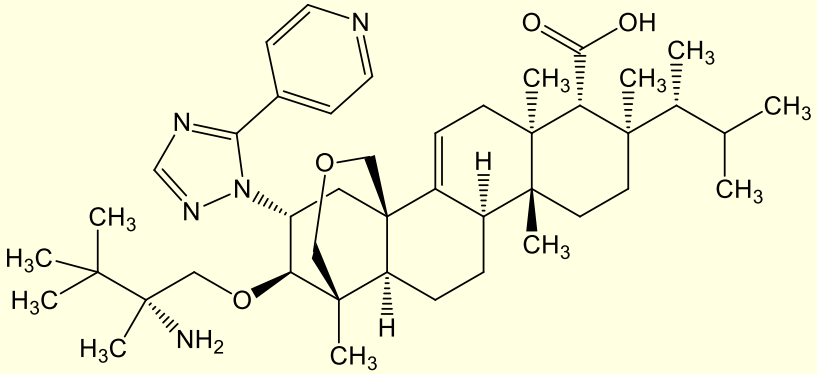
Natural products, their derivatives and mimics comprise greater than 50% of all clinically used drugs

Natural Products (~300K)
The Gift that Keeps on Giving

Today over 80% of the world's population relies on traditional medicines to maintain health and treat diseases and symptoms

- From **1981 to 2008 a total of the 1024 drugs** that were registered, the following is the impact of ongoing natural product-driven drug invention: 6% were natural products, 27% were natural product derivatives,12% were natural product mimics, 5% had natural product pharmacophores, 13% were natural product pharmacophore mimics thus **63% were natural product-based – only 37% drugs were totally synthetic-based compounds in origin;** ~6% of all drugs approved by the FDA are natural products including some mixtures
- For cancer drugs alone, the numbers are 17%, 31%, 4%, 12%, 10% respectively with only 26% originating as non-nature-based synthetic entities
- **For insecticides - ~80% are natural products or natural product derived – bioactivity everywhere**
- In 2010, 50% of the 18 small molecule drugs approved by the FDA were natural product-based or influenced

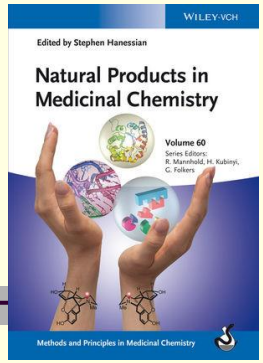
Ibrexafungerp – semisynthetic triterpenoid **oral** anticandidal agent approved in 2021; one of nine (**18% of NCEs**) natural product-based drugs approved in 2021;**Three (8% new natural product-based drugs were approved in 2022**



- **The major classes of natural product-based dugs**
  - *Neurologic* agents like morphine, atropine, curare, tetrahydrocannabinol, caffeine, physostigmine
  - Anti-infective agents like the β-lactams, macrolides, aminoglycosides, nucleosides, tetracyclines
  - *Antitumor* natural products like the vinca alkaloids, taxanes, anthracyclines, cytarabine, mitomycin
  - Anti-inflammatory drugs like the corticosteroids, prostaglandins, leukotrienes, salicylic acid
  - Hormones/vitamins like the sex steroids, vitamin D, retinoids, insulin, GLP-1, thyroxine
  - CV drugs like the statins, ACE inhibitors, heparin, niacin, digitoxin, coumadin, ergotamine
  - Other drugs like *N*-butyl-deoxynojirimycin, phlorizin, stevioside, Capsaicin

Novel Intractable Target or Mechanism of Action: Who are You going to Call?

Call 1-800-Natural Products Chemists



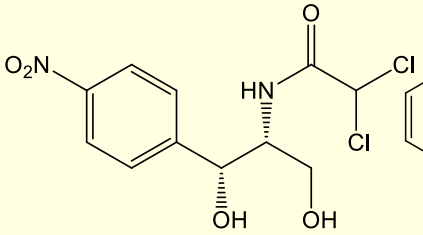
- **Advantages**
  - Predisposed to interaction with biological systems due to evolutionary pressure in the host (or the hosts' food sources) to generate and optimize their specific biological function
  - **Novel, unforeseen molecular targets and mode of actions, including *polypharmacology***
  - High potency, dramatic activities,(weird) biocompatible physicochemical properties
  - **Most diverse source of small molecules including novel feature like - medium sized molecules, highly functionalized (lots of oxygen and nitrogen functional groups embedded in their structures) scaffolds, reactive functionality, conformational plasticity, chirality, multitude of sp^3 atoms and *esthetically beautiful three-dimensional architectures***
  - ***Molecules that regularly violate the sanctity of the sacred rules of medicinal chemistry***
  - **A long history and strong track record of successful novel drug origination**
- **Challenges**

  - **Limited supplies, small quantities available, exotic sourcing**
  - Limited by biosynthetic pathways and natural sources
  - Limited by synthetic feasibility
  - **Analog development is typically limited to derivatives (morphine being a big exception)**
  - Historically screening limited to cytotoxicity in cancer cells and anti-infectious disease surveys. However, as statins and immune suppressants demonstrated, screening outside traditional medical indications can lead to enormous financial success
  - Commercial manufacturing can prove to be quite problematic and expensive
  - **Limited expertise remains in industry and unfashionable drug science since the 1980s**
  - The Convention on Biological Diversity created substantial hurtles and disincentives to natural product mining

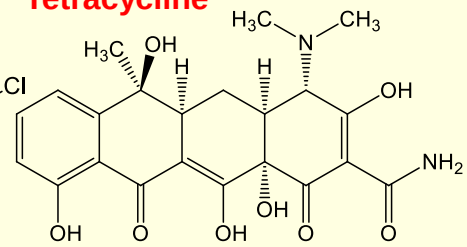
Some Old Natural Product Drugs that Changed the World

I and many of You Exist Today because of the Discovery of the Antibiotic Drugs

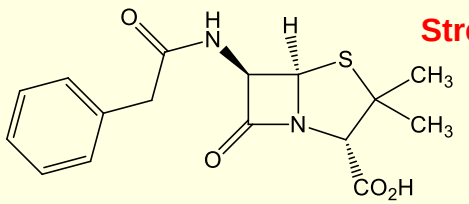
Chloramphenicol



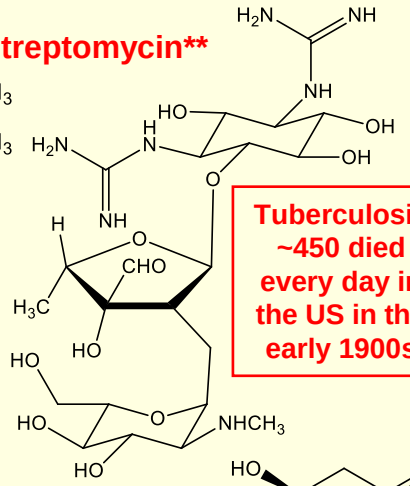
Tetracycline



penicillin G**



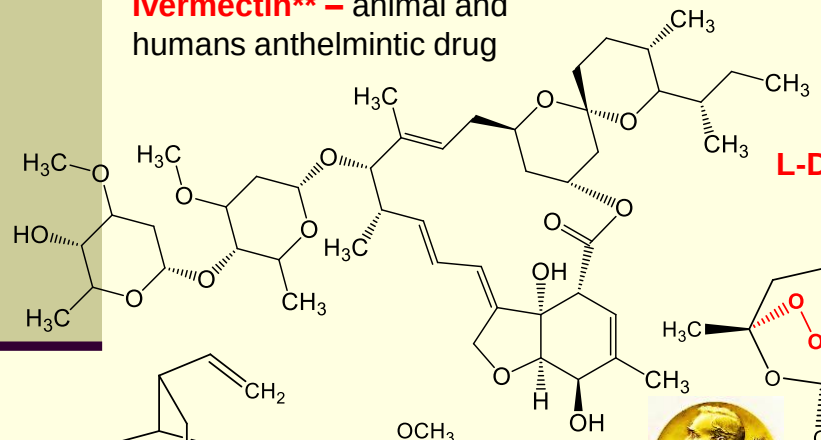
Streptomycin**



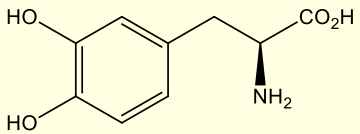
The antibiotics - vanquished death by bacteria and emptied the TB sanatoriums

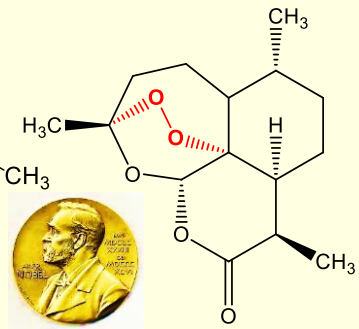
Tuberculosis ~450 died every day in the US in the early 1900s

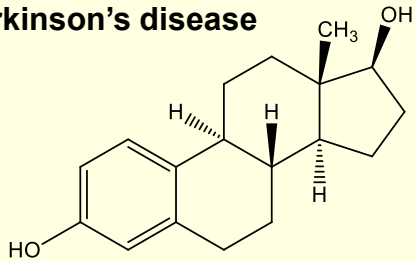
Ivermectin –** animal and humans anthelmintic drug



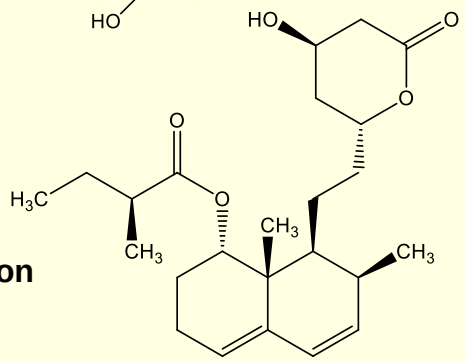
L-DOPA* – Parkinson's disease

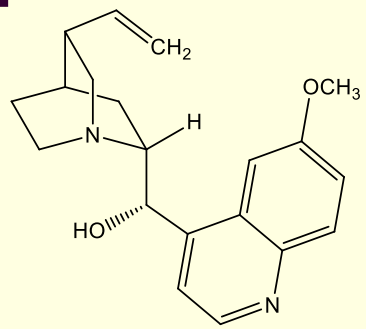






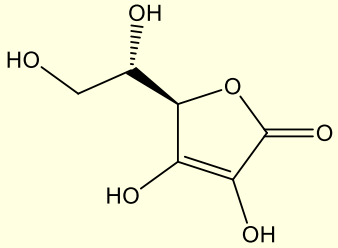
Estrogen - contraception**





Quinine – 1st antimalarial drug

Artemisinin - newest ancient antimalarial drug from traditional Chinese medicine. Undevelopable in modern times. Why? Multiple in vitro/vivo (un)safety signals issues**



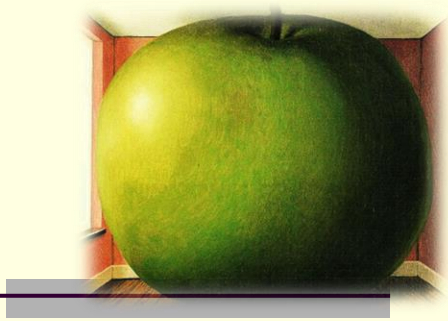
Vitamin C - scurvy**

Compactin* – 1st statin hypolipidemic agent originated in 1971

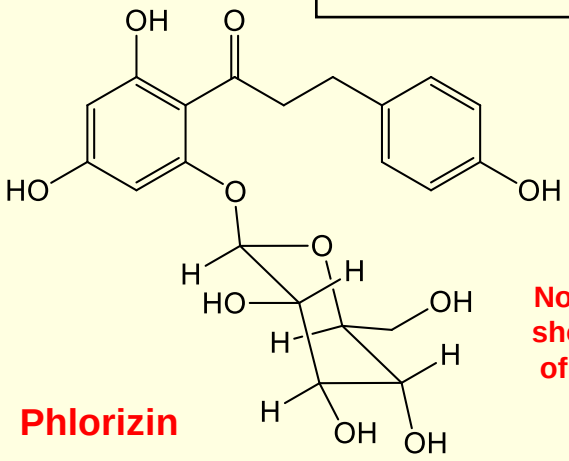
**Nobel Prize
*Wolf Prize

Example of a Recent Natural Product-Derived Drug

Natural Product Mimics



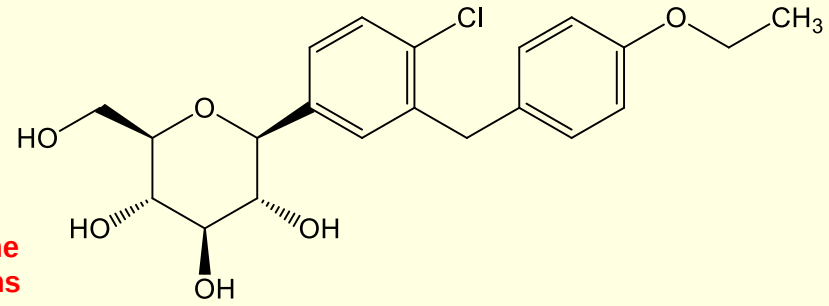
An example of the very long and winding road of Natural Product *drug discovery*



Phlorizin

180 years

Not compatible with the short-term expectations of medicinal financiers



Dapagliflozin – BMS-AZ (FDA approved **2014** – for glucose control in T2 diabetics)

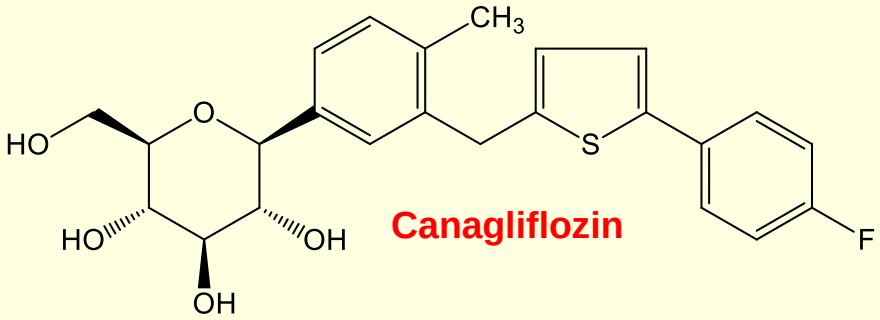
Phlorizin (**1834**) from root bark of apple trees – **Von Mering** demonstrated the glucosuria activity for phlorizin in **1886**. In the **1980s**, it was shown that this molecule worked by **specifically blocking reuptake of glucose in kidneys by inhibiting the** **S**odium/**Gl**ucose co-**T**ransporter (**SGLT1/2)** - ***a potential antidiabetic drug target***

K_i = 151nM and 19nM respectively

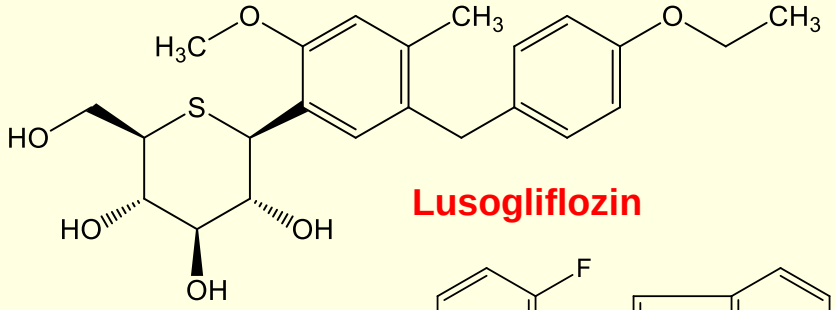
Targets are only fully de-risked with the regulatory approval of the 1st in class drug addressing that target, then all the me-betters all pile in behind

Phlorizin Analogs - I Want One of Those! Or How to Win in Big Pharma

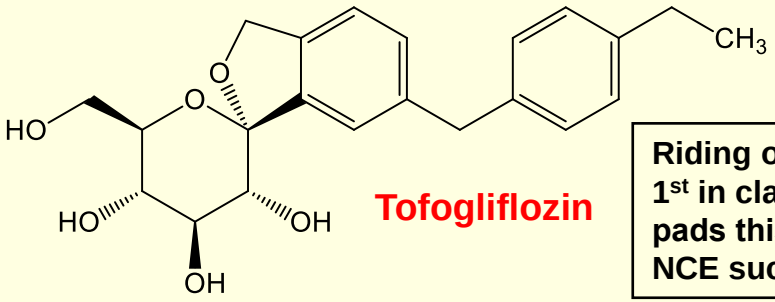
It's What We Chemists do for a Living



Canagliflozin

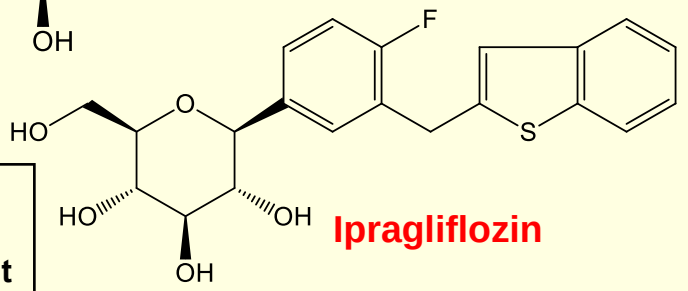


Lusogliflozin

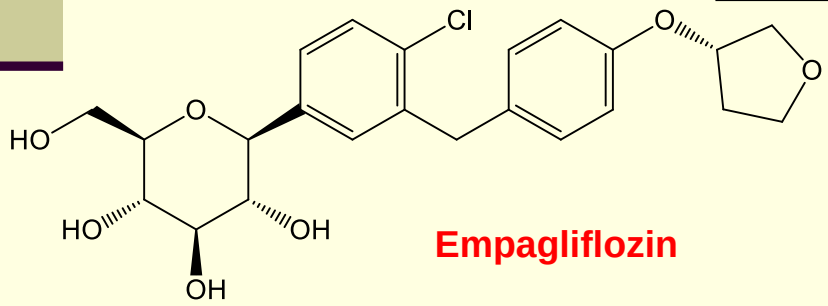


Tofogliflozin

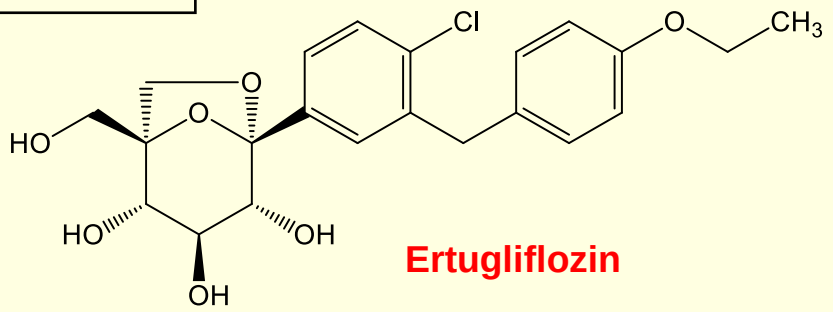
Riding on the coattails of a 1st in class success greatly pads this industry's modest NCE success track record



Ipragliflozin



Empagliflozin



Ertugliflozin

The ME-TOOs – Best in class, fast followers, differentiators and latecomers (1991-2000) all showed higher risk-adjusted values than the truly novel first in class drugs. Risk taking is rewarded less than a follower strategy. This is driven primarily by the failure-risk profile for a first in class drug in the clinic

The Rule-of-5 and Other Rule-Based Predictive Tools for (Oral) Bioavailability are Actually Just Suggestions

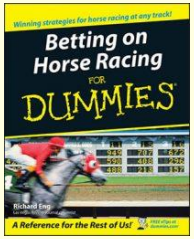
These are Not Commandments Handed Down by the Almighty on High

Realistic boundary conditions for oral drug absorption

- **For useful >5% oral bioavailability boundaries based on multiple surveys of orally bioavailable compounds**
  - **MWT ≤1000 Da**
  - **PSA ≤250 Å**
  - **Clog P range ≥-2 to ≤10**
  - **HBA ≤ 6**
  - **HBA ≤15**
  - **Rotatable bonds ≤20**
  - **Transporter-mediated oral availability can totally change the equation**

Predictive Computational Tools can be Excellent at Predicting the Past
It's just like handicapping the ponies

I have never seen a theory so compelling to justify not running the experiment – Nobel Prize winning Chemist R. B. Woodward



If you are going to make up defining rules for drug discovery, you cannot simply ignore natural product drugs, as Lipinski did, because these drugs invalidate your cutesy rules

Natural products can have chameleon-like features as their complex, flexible structures can change shape and their exposed polar features as move from water to lipid and back again allowing them to adapt to their environments and escape rule-based boundaries. This is made even more unpredictable if transport mechanisms come into play for both natural products and synthetic drugs

Drug-Like Properties of Anticancer Natural Product Drugs Addressing Intracellular Molecular Targets

While the Bioengineers have been Focused on Curing Cancer with Injectable Drugs, We Medicinal Chemists have been Mesmerized by Oral Bioavailability

Cancer Drug (Target)	MW	HBD	HBA	PSA	Route	XLogP
Doxorubicin (TPO II)	544	6	12	206	Oral/IV	1.3
Romidepsin (HDAC)	541	4	8	193	Oral/IV	2.2
Neocarzinostatin (DNA)	662	4	13	175	IV	2.3
Vinblastine (Microtubule)	811	3	12	154	IV	3.7
Paclitaxel (Microtubule)	854	4	14	221	IV	2.5
Rapamycin (mTOR)	914	3	13	195	Oral	6
Chromomycin A3 (DNA)	1183	8	26	359	IV	2.3
Actinomycin D (DNA)	1255	5	18	356	IV	3.8
Bleomycin (DNA)	1513	21	29	770	IV	-1.9
AVERAGES (longer list)	**700**	**4.9**	**12.6**	**208**	**--**	**1.8**

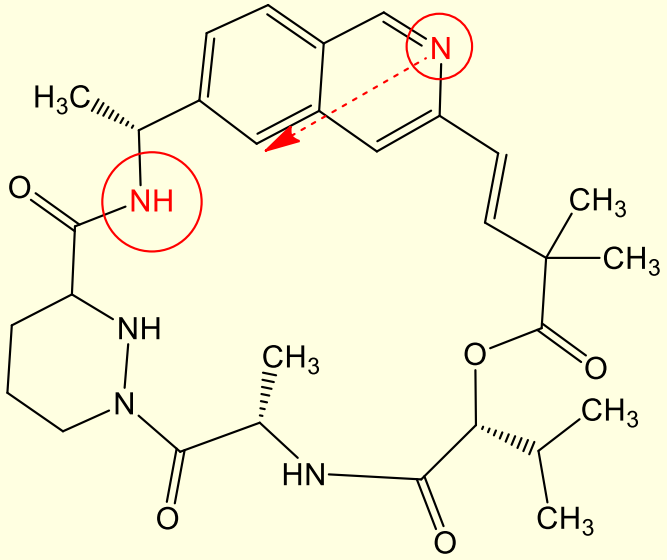
The useful *Rule of Thumb* (RoT) for natural products drug discovery: keep logP under 4 and HBD under 5

Natural products bring novelty, selectivity and potency in leads, but can be associated with sourcing, solubility, stability and Isolation challenges. However as history teaches, these problems can all be overcome via novel formulation, bio/synthesis production techniques, and modern isolation technology.

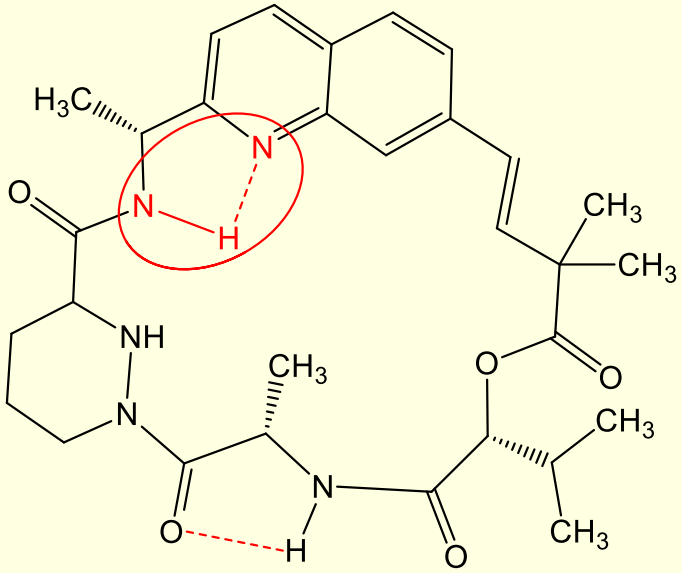
Improving Membrane Permeability

Internal Hydrogen Bonds Can Enhance "Drug-Like" Properties about 50% of the Time – Something NOT Captured in Simple Counting Rules

If simply counting atoms was all that chemists needed to do to invent drugs, we chemists would all be Gold Metal winners in this game



Without an internal hydrogen bond:
Log *D* = 2.0 (pH 7.4)
Caco-2 flux AB/BA = 0.1/7.9 10^{-6}cm^{-1}
Solubility 6μg/mL water

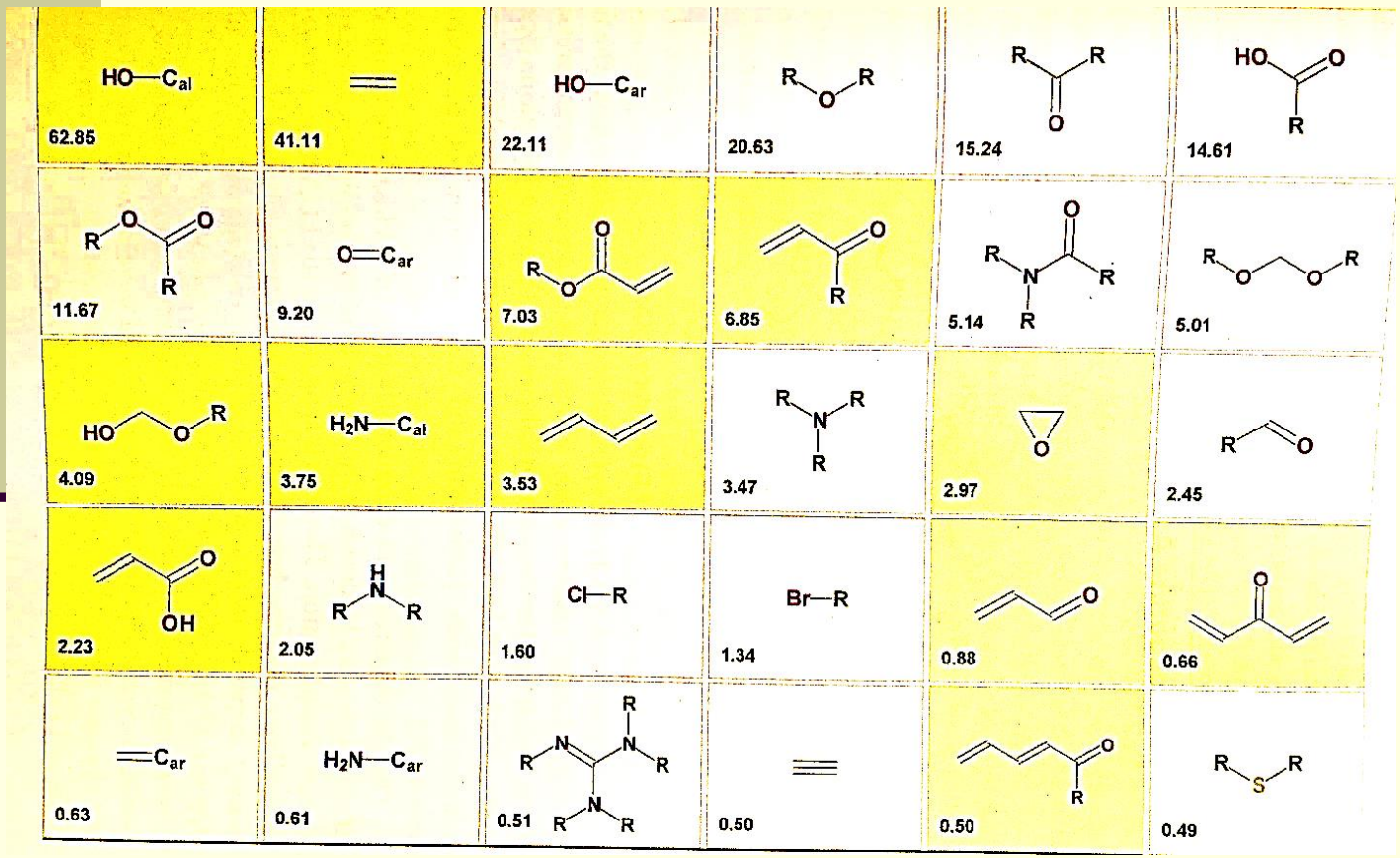


With an internal hydrogen bond:
Log *D* = 3.2 (pH 7.4)
Caco-2 flux AB/BA = 17/47 10^{-6}cm^{-1}
Solubility 55μg/mL water

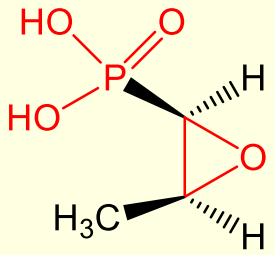
"Subtle is the Lord, but malicious He is not. I have second thoughts. Maybe God is malicious"

Most Common Chemical Functionality Found in Natural Products – It's a Very Different World

Numbers indicate percentages of natural products containing the specific functional group and **yellow colored shading are functional groups appearing more than 5 times the rate they appear in synthetic molecules**



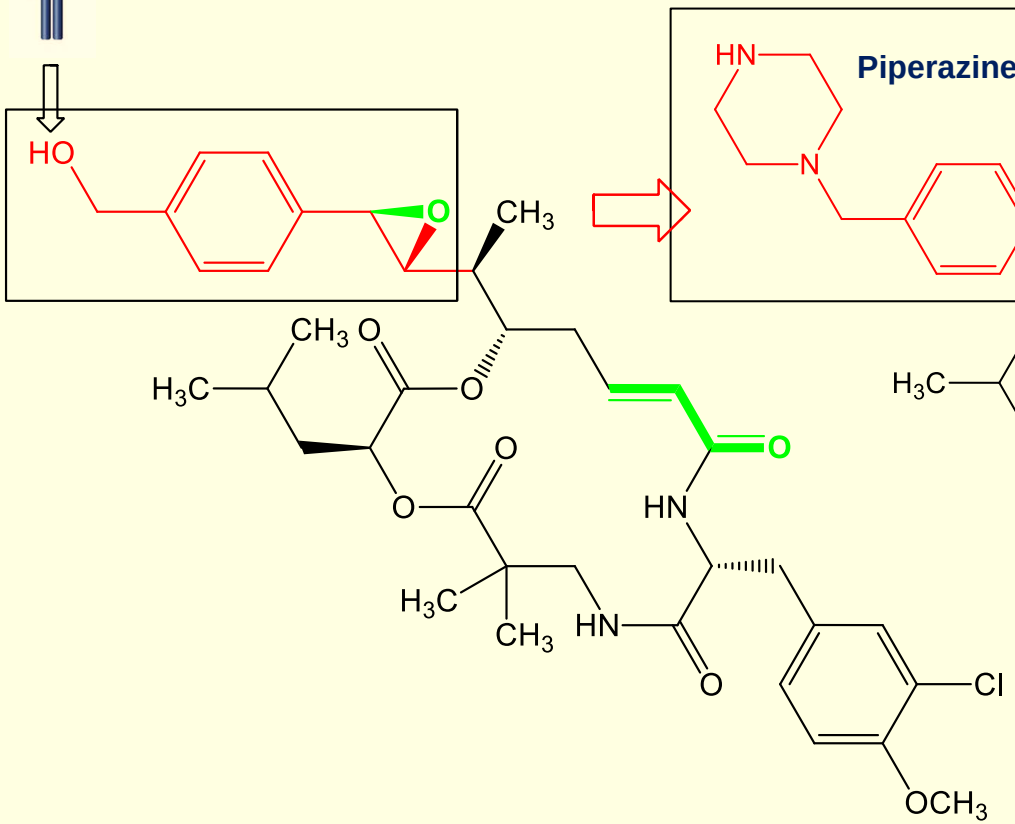
5% of FDA approved drugs (both synthetic and natural) would set off PAINS (pan interference) screening alerts

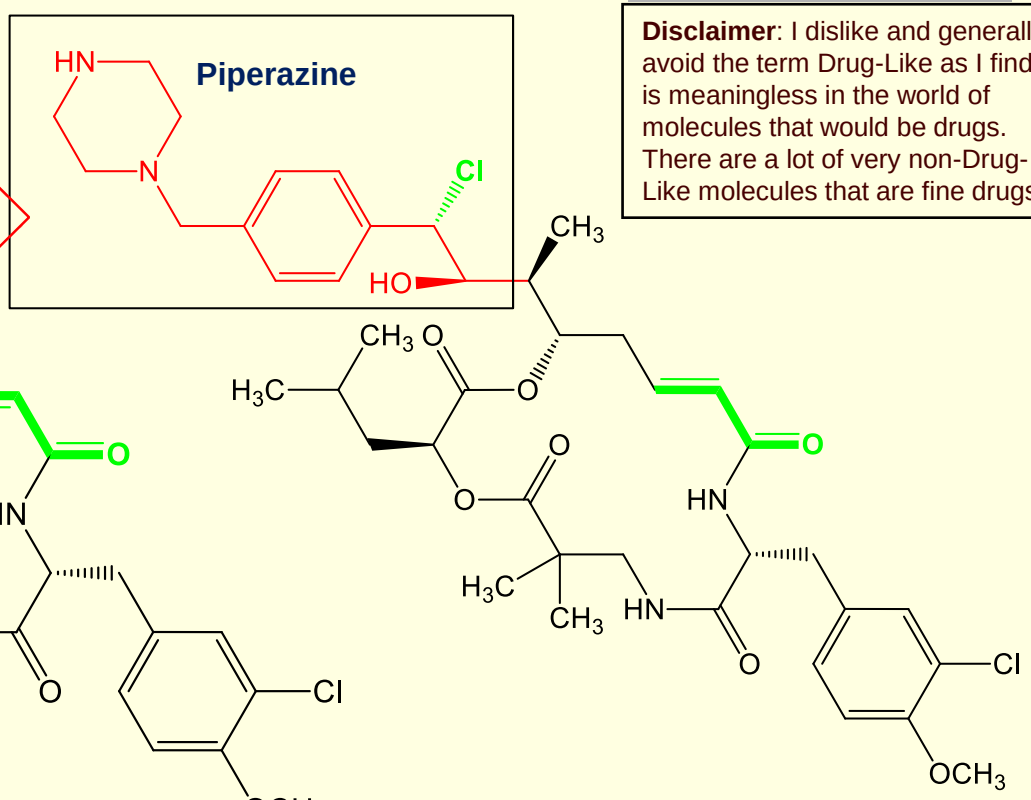


Fosfomycin, antibiotic, MW = 138; Log P= -1.6; highly water soluble; $T_{1/2}$=1.7h; **oral bioavailability = 33%**
Epoxide/phosphonic acid
PO dose: 3gm

Great Potency Allows You to Give Back Some in the Name of More Desirable *In Vivo* Properties

Disclaimer: I dislike and generally avoid the term Drug-Like as I find it is meaningless in the world of molecules that would be drugs. There are a lot of very non-Drug-Like molecules that are fine drugs.





Cytotoxic Natural Product
CC_{50} = 4 picomolar
Very weak in vivo activity
low solubility
MW = 698.5

Greater Target potency can pay for a lot of Drug-Like properties sins

Cytotoxic-antitumor NP analog
CC_{50} = 21 picomolar
Highly active in vivo
high solubility
MW = 803 (*a Rule of 5 no-no*)

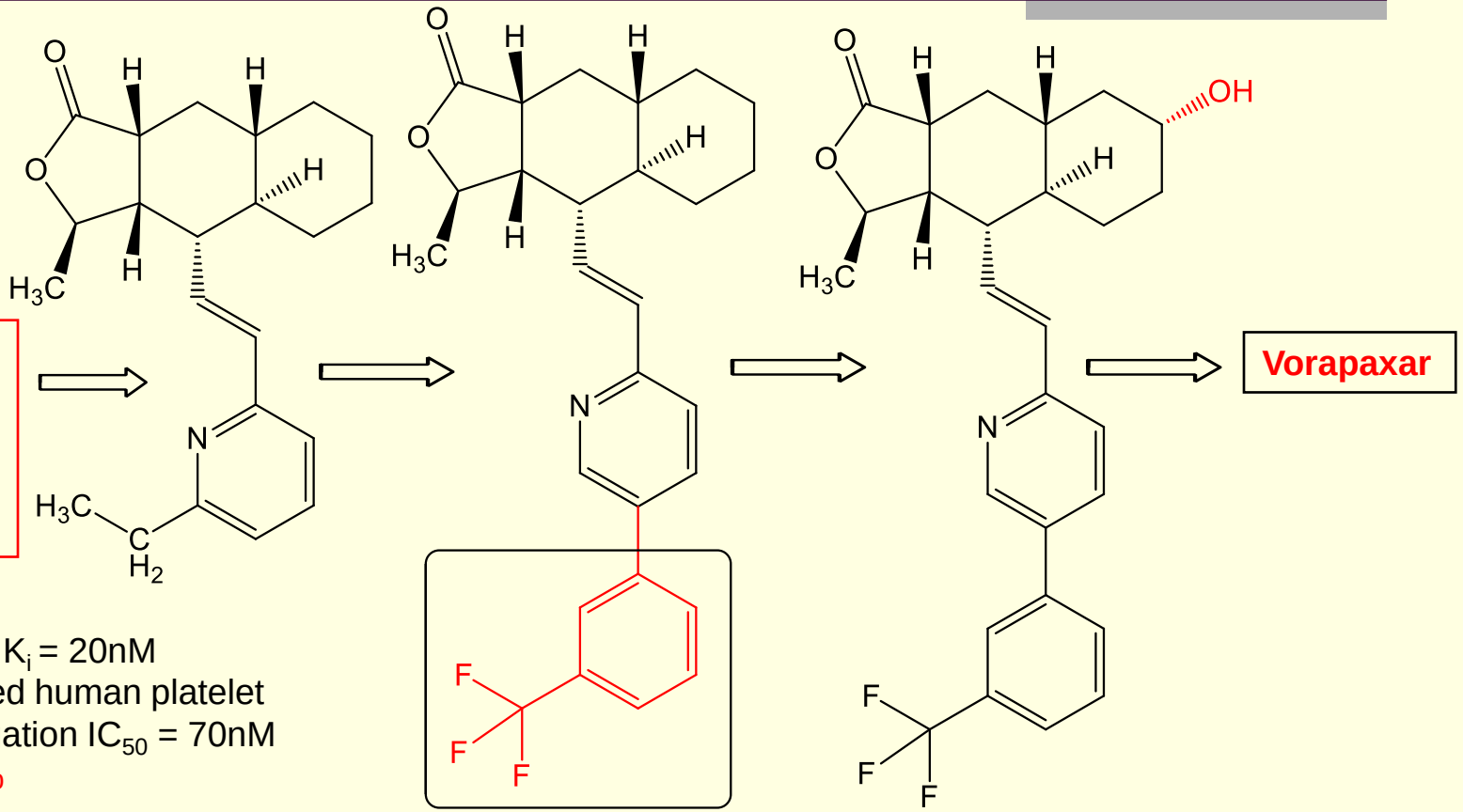
Optimization of the Lead

Forty Medicinal Chemist-Years over Six Years and Multiple Series

Thrombin Receptor, a Protease-Activated Receptor -1 (PAR-1)

Racemic Himbacine - a M2 muscarinic receptor antagonist - analog screening hit

Exploiting collateral activity for profit



- PAR-1 K_i = 20nM
- Inhibited human platelet aggregation IC_{50} = 70nM
- *F* = 3%

- PAR-1 K_i = 2.7nM
- Inhibited human platelet aggregation IC_{50} = 44nM
- *F* = 50% (monkey)

- PAR-1 K_i = 11nM
- Inhibited human platelet aggregation IC_{50} = 60nM
- *F* = 89% (monkey)

Medicinal Chemistry is not for those with short attention spans and low tolerance for repeated failures

Macrocyclic Compounds

The Precious Rings that Bind Them All

Either via Edge-On or Simple Blanketing Interactions

- **Macrocycles 10 – 40 atom rings occupy the "Middle Space" (MW >500 - <2000) between traditional small molecules and biologicals – macrolides, cyclic peptides, ansamycins, porphyrinoids, cyclodextrans, cembranoids…. The quest for macrocyclic drugs is in fashion**
- 11,000 natural macrocycles are reported in the natural product literature ~5%
- 95% of marketed macrocycles are natural product derived and >50% target infectious diseases
- **30% of marketed macrocycles are orally administered**
- Macrocyclization (including disulfides) with their diverse functionality and defined topology can provide improved potency, greater selectivity and a larger protein binding surface for addressing difficult intractable drug targets like those involving protein-protein interactions, major grooving binding surfaces on DNA and protein binding receptors
- Macrocyclization can mask metabolic soft spots to increase half-life, reduced molecular flexibility, proteolytic liabilities, mask and unmask hydrogen binding functionality to alternatively enhancing solubility in aqueous and lipid environments (buried H-bond donors), and enhance oral bioavailability **– a survey of 184 macrocycles showed that 22 had human oral availability and 168 (91%) show rat oral bioavailability - 28% of which had *F*>30%**
- For cyclic peptides, N-amide alkylation (methyl) can enhance oral availability (or not); around **40 cyclic peptide-based drugs are in clinical use** and more on the way
- Intramolecular H-bonding and lipophilicity can enhance oral availability of macrocycles
- Ro5 compliance is somewhat optional and **paracellular absorption is possible even for large macrocycles - 67 marketed and 35 clinically tested macrocycles are Ro5 noncompliant**
- Orally dosed macrocycles cLogP values: 4.4, whereas parenteral macrocycle values: 2.1
- **Orally dosed macrocycles have molecular weight ranges of 500 to 1500 Daltons**

A Super Obese Macrolide from a Sea Hare can Facilely Cross Cell Membranes and Displays Excellent In Vivo Efficacy

I am Structure Agnostic, In Vivo Bioactivity Pragmatic

Aplyronine A (from a Japanese sea hare) - inhibits polymerization of G-actin to F-actin and depolymerized F-actin from G-actin.

Cell cytotoxicity IC_{50} = 39 pg/mL

In vivo antitumor activity:

P388 murine leukemia	**T/C – 545%** at 80μg/kg
Lewis lung carcinoma	**T/C – 556%** at 40μg/kg
Ehrlich carcinoma	**T/C – 398%** at 40μg/kg
Colon 26 carcinoma	**T/C – 255%** at 80μg/kg
B16 melanoma	**T/C – 201%** at 40μg/kg

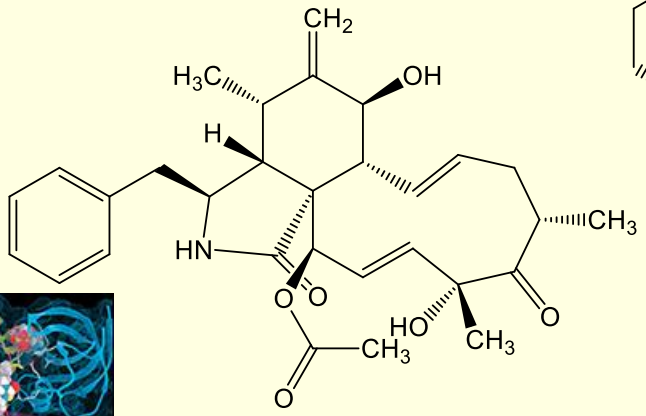
Our quest is to conquer disease and alleviate symptoms. In the end, how we achieve these goals matters little to the patients we cure and/or comfort

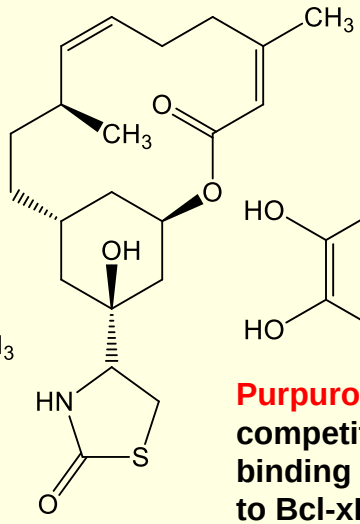
The Key Question: why isn't it a drug?

Protein-Protein Interactions (~650K)

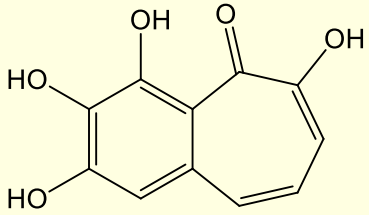
Breaking up Is Hard to Do, but With Natural Products There Are Fifty Ways to Leave Your Lover (or Stick to Your Lover)

Cytochalasin D and Latrunculin A– G-actin binding assembly inhibitor - capping – reduces intraocular pressure

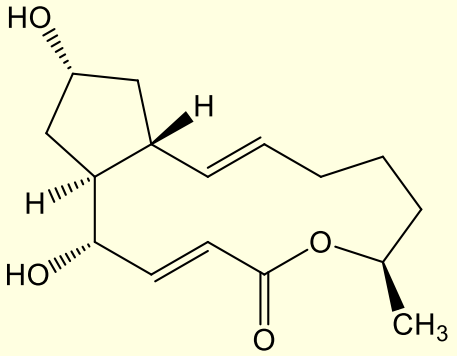


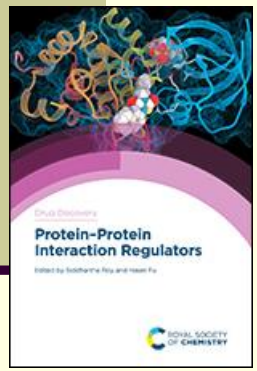


Purpurogallin- competitive inhibitor of binding of BH3 peptide to Bcl-xL; K_i=2.2μM



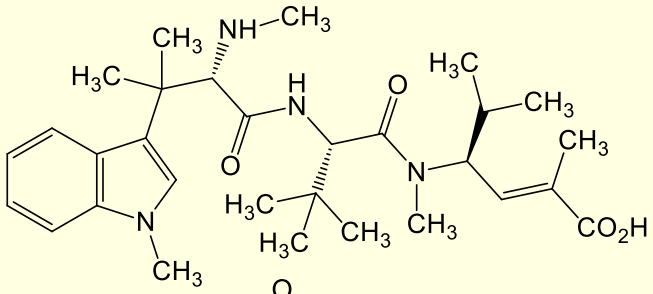
Brefeldin A – ARF1/ARNO-guanine exchange factor binding stabilizer blocking GDP/GTP exchange



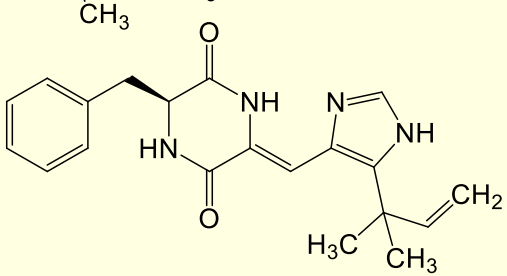


PPI typically cover ~1500 to 5000 Å² with a 600 Å² binding hot spot (antibody complex buries ~ 800+/- 200 Å² surface area), ~0.01% targeted to date

Hemiasterlin – peptide binding site tubulin polymerization inhibitor



Phenylahistin – novel a/b tubulin interface binding site tubulin polymerization inhibitor



Molecular PPIs and Glues:

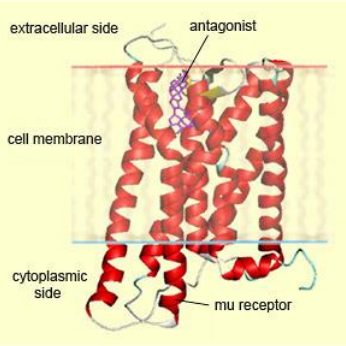
- Direct and allosteric antagonists
- Agonists-activating cofactors
- Signaling hub poisons
- Inhibitors of degradation
- Facilitator of degradation
- Sequestrants
- Trafficking inhibitors
- Trafficking facilitators
- Localization inhibitors
- Chaperones/anti/re-foldamers
- And ….

μ-Opioids - God's Own Medicine

Stanford's Dean Pizzo: "There is an under-appreciation of the need for optimal pain control"

Curing the source of pain is great, but in the mean time can I get relief from my awful PAIN symptoms?!

- Opium (Greek = poppy juice) known and used in the Old World for last 5000 years; Source of great wealth for East India Co.; origin of the Opium Wars between China and Britain; and in 19th century opium transitioned from a medicine to a recreational substance of abuse
- Tinctures of opium – laudanum was a Middle Ages medicine
- Alkaloid morphine (after Morpheus, servant of sleep and creator of dreams) isolated from opium in 1805
- **Prodrug Heroin was introduced by Bayer in 1898 as a safer morphine** which it was not, but rapidly became the drug of choice among US addicts the preparation was made illegal in 1924 **commencing the 100-years NARCO Wars**
- **Opioids exert their biologic effects by binding to the μ–opioid receptor** discovered in 1973 by Candace Pert and Solomon H. Snyder
- **The opioid receptors are GPCRs**
- δ, κ, ζ, and NOR opioid receptors also found to exist. **A κ–agonist for itch - 2021**
- The natural hormones for μ-receptor are the **endorphins** and the endomorphins
- **Synthetic opioid analog chemistry commenced with the preparation of Demerol in 1939 at IG Farben and it continues to this day**

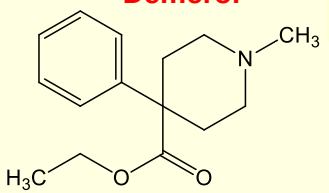


μ–opioid receptor

Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu

β-endorphin (Met enkephalin)

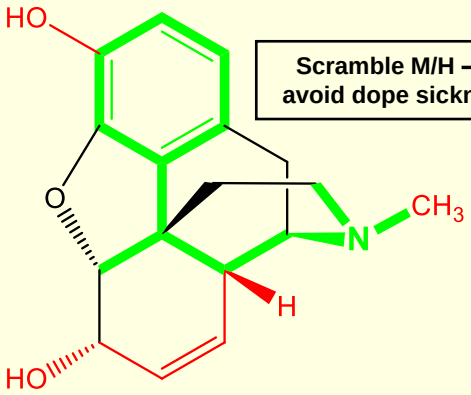
Demerol



Morphine Medicinal Chemistry in Action

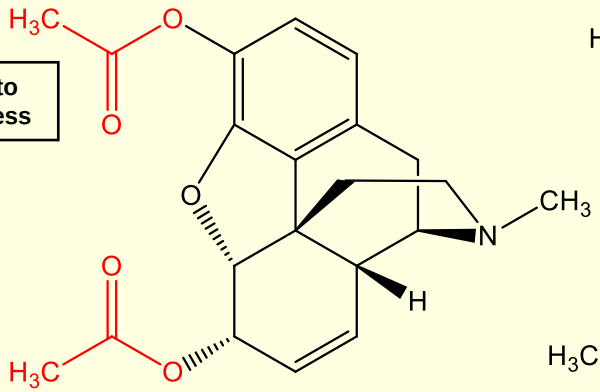
A Handful of the 10,000s of Potential Designer μ-Opioid Drugs

Pharmacophores: the common structural denominator of a group of molecules exhibiting a similar pharmacological profile and which is recognized by the same site on a target protein

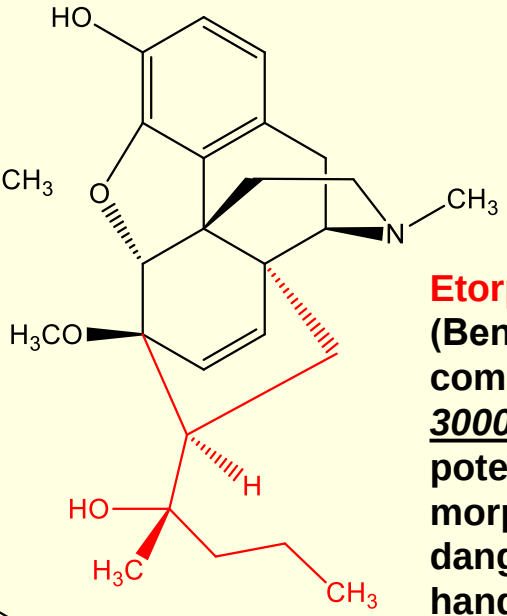


Scramble M/H – to avoid dope sickness

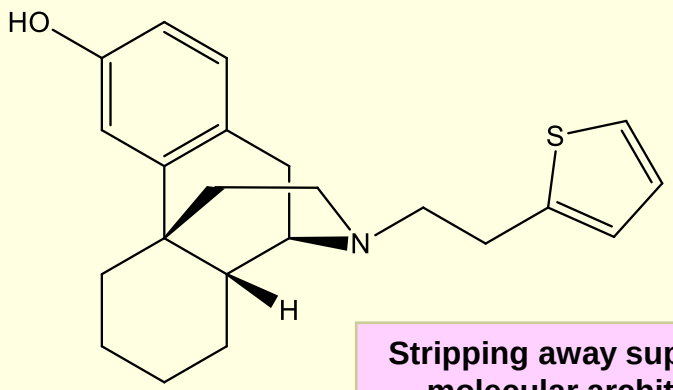
Morphine - Brain Uptake ~2%



Prodrug Heroin - Brain Uptake ~65% - the first designer opiate

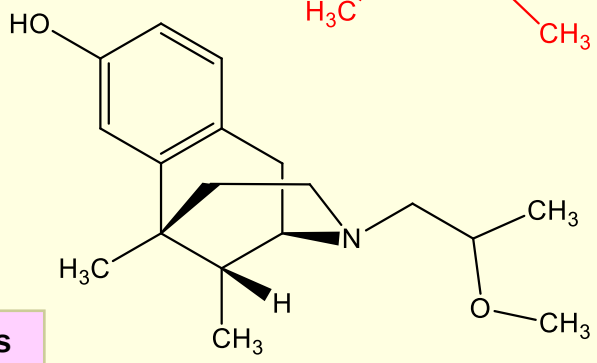


Etorphine (Bentley's compounds) *3000X* more potent than morphine –very dangerous to handle; 1 mg can bring down an elephant, *Immobilon*®



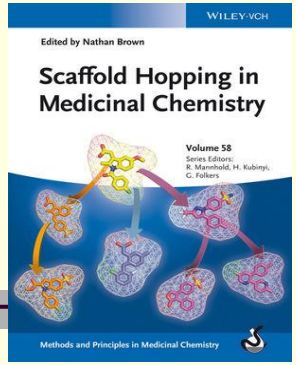
Morphinans (*100X*) (related to krokodil)

Stripping away superfluous molecular architecture

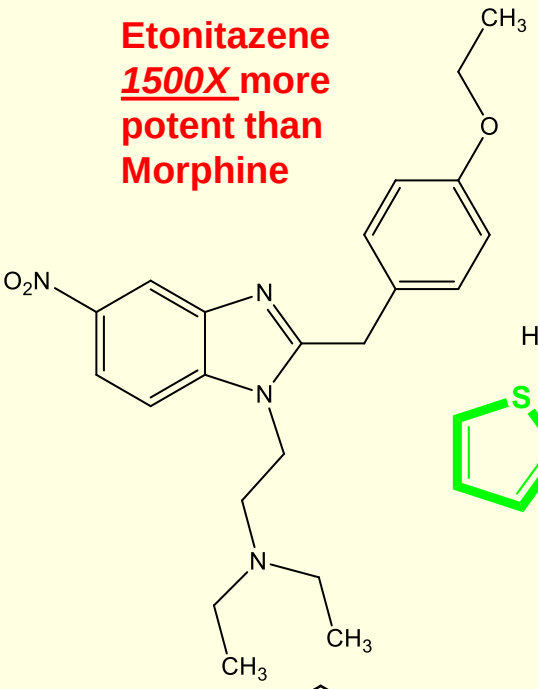


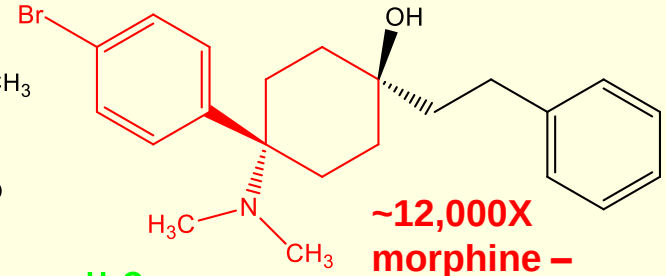
Benzomorphans (*100X*) (Talwin - Ts and Blues)

Novel μ-Opioid Binding Scaffolds: I have only Scratched the Surface

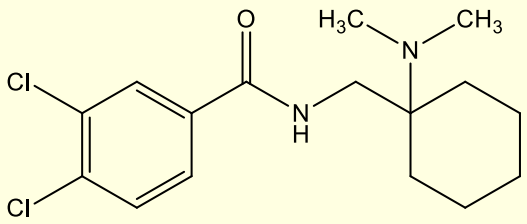


Etonitazene *1500X* more potent than Morphine

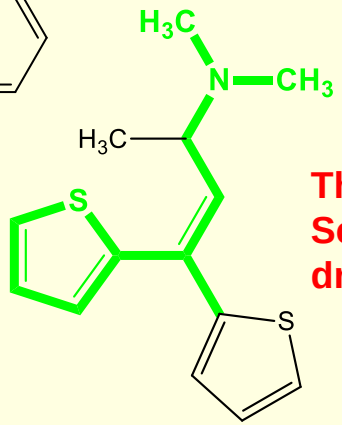




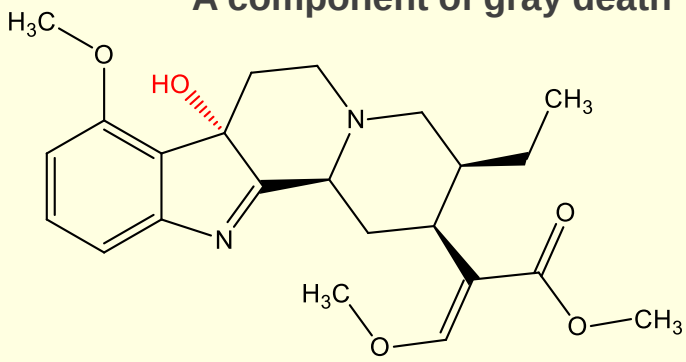
~12,000X morphine – (PCP analog)

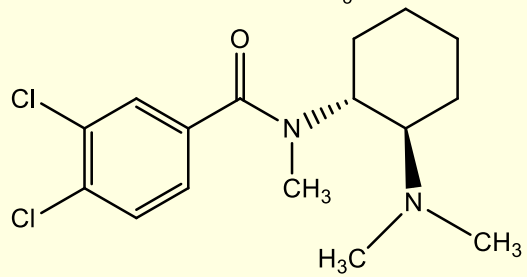


AH-7921 (~morphine)
A component of gray death

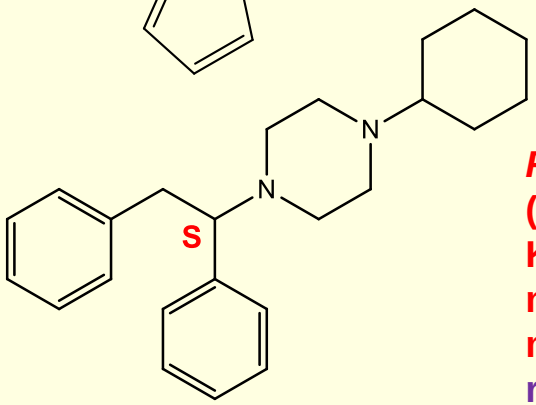


Themalon Schedule 1 drug in USA





U-47700 (~8X morphine)



MT-45 (S-isomer ~morphine)

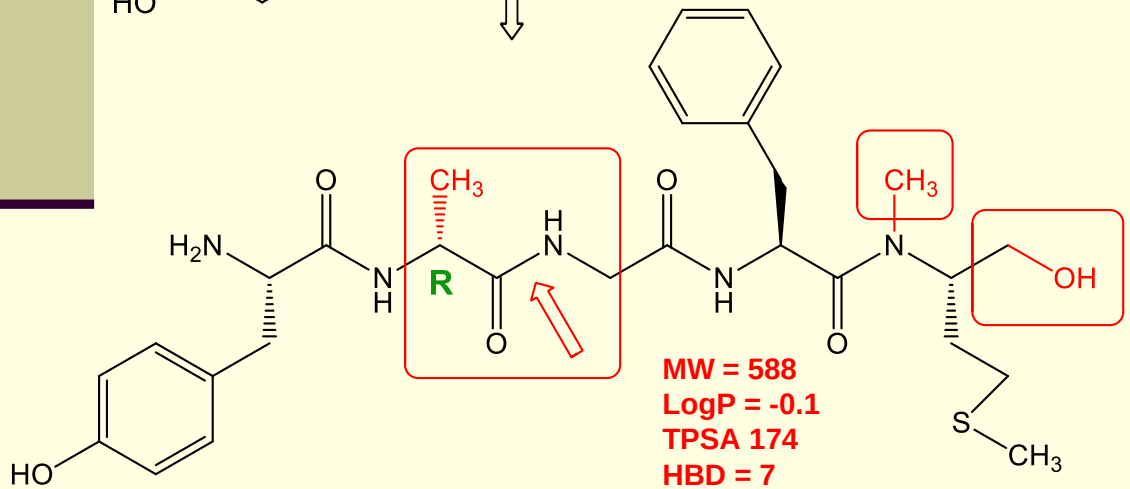
***RelaKzpro* - Hydroxymitragynine (metabolite) from Thailand plant Kratom (X17 morphine) -- the newest plant-derived non-morphine morphinoid; does not recruit β-arrestin – biased agonist**

Turning Peptide Leads into Drugs

Sir James Black: "The most fruitful basis for the discovery of a new drug is to start with an old drug"

Met enkephalin
Half-life in minutes

Peptide medicinal chemistry in action



MW = 588
LogP = -0.1
TPSA 174
HBD = 7
HBA = 11
Rot bonds= 16
N+O = 11

RoThumb *for cell membrane penetration by peptides and small proteins from observations on venoms and toxins*

- **Cationic (>2+ charges)**
- **Small size <40 amino acids**
- **Low MWT <5000Da**
- **High basic AA content (Arg &Lys)**
- **Anionic and neutral charge negatively impact cell permeability**

Peptide drugs typically display very high potency and low clearance

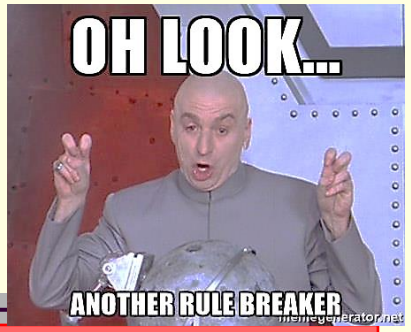
An acceptable therapeutic window is 10-fold for protein drugs. A number of small peptides pass through the BBB by using saturable transported systems these include insulin, amyloid-β, arg-vasopressin

Met enkephalin analog which displays in vivo analgesic activity, with potency and an efficacy half-life (~2hrs) comparable to that observed for morphine – both drug administered by s.c. injection

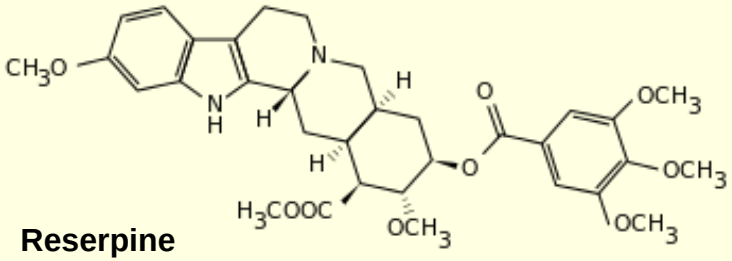
Obviously, this peptide crosses the BBB despite lots of BBB passage rule violations

Large NP CNS-Active Molecules that Cross the Blood Brain Barrier

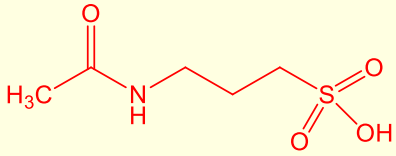
Are the Chemists Being Too Clever by a Half?



Violating the BBB Accessibility Rules : PSA <70Å², MW<450, Not acidic, O+N < 5

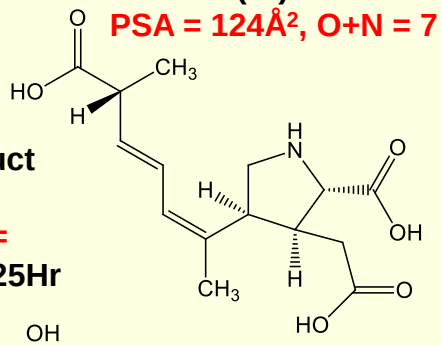


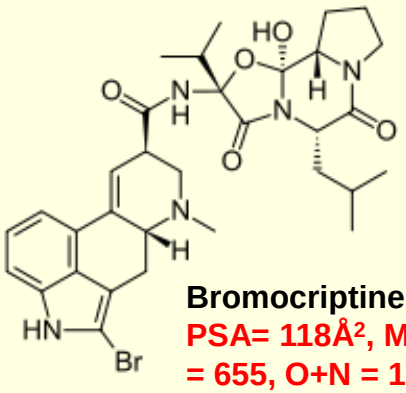
Reserpine
PSA = 118Å², MW = 609, O+N = 11



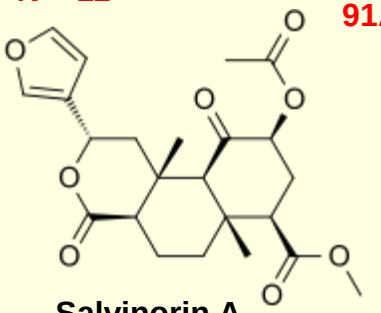
Acamprosate (marine natural product derivative for treating alcohol dependence) - sulfonic acid! PSA = 91Å², O+N = 5; PO BA 11%; $T_{1/2}$ = ~25Hr

Domoic (tri)acid
PSA = 124Å², O+N = 7

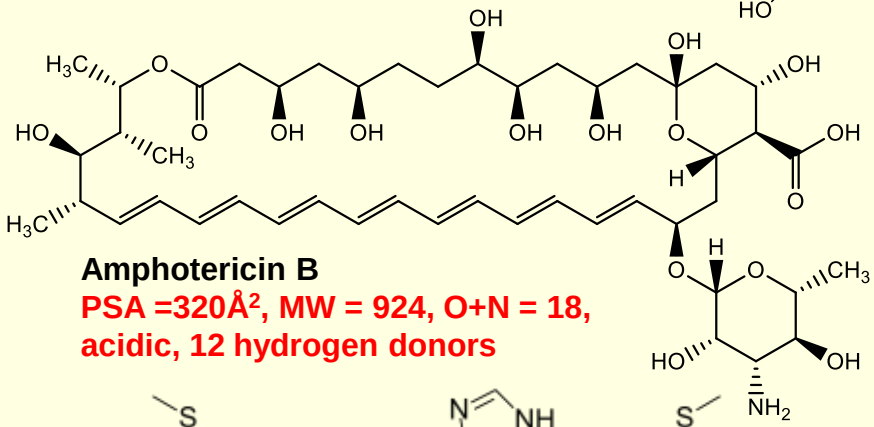




Bromocriptine
PSA= 118Å², MW = 655, O+N = 10

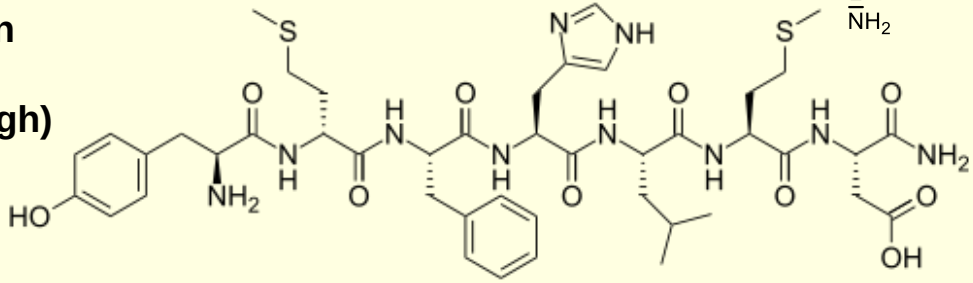


Salvinorin A
PSA = 109Å², O+N = 8
Psychomimetic κ-agonist

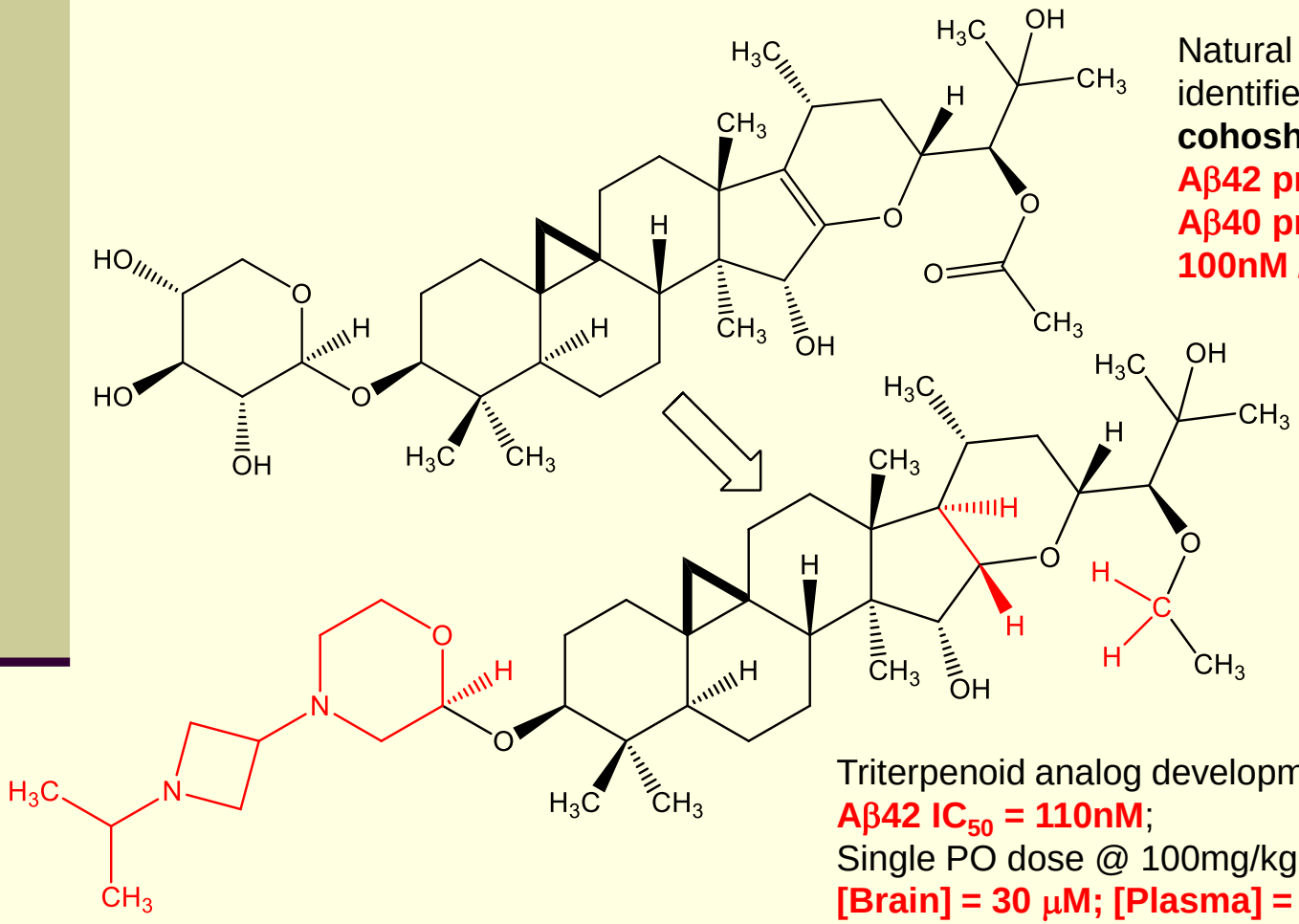


Amphotericin B
PSA =320Å², MW = 924, O+N = 18, acidic, 12 hydrogen donors

Deltorphin δ-opioid (Sapo secreation from frog skin - crosses small skin wound and enters brain for a >4h high)
PSA= 381Å², MW = 955, O+N = 40, acidic, 13 hydrogen bond donors, abusers don't care about BBB rules



The Magical Biology of Natural Products - Selective Modulators of Aβ42 Production (Gamma Secretase Inhibitor)

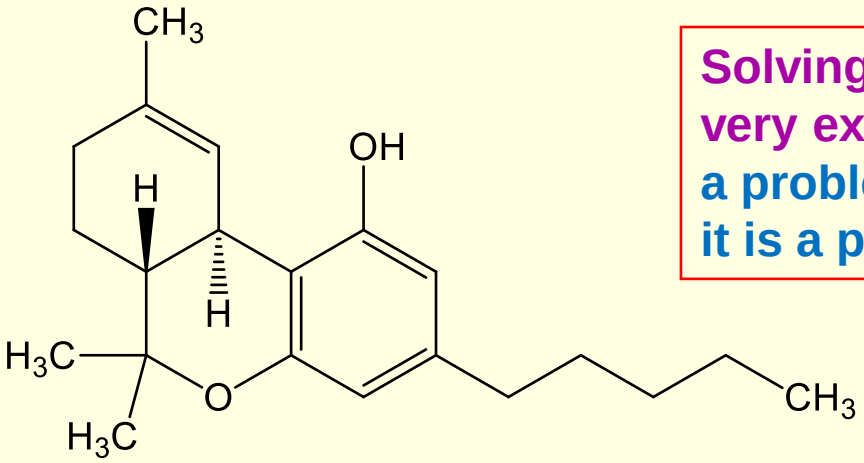


Natural Product cell-based screen identified triterpenoid in **black cohosh** that **lowered pathologic Aβ42 production while sparing Aβ40 production; Aβ42 IC_{50} = 100nM / Aβ40 IC_{50} = 6300nM**

Triterpenoid analog development candidate **with CoM IP**
Aβ42 IC_{50} = 110nM;
Single PO dose @ 100mg/kg lowered Aβ42 levels 50%
[Brain] = 30 μM; [Plasma] = 14μM
Multi-PO dose @ 60mg/kg lowered Aβ42 levels 66%
Halted clinical development - *adrenal function issues*

THC - One Natural Product that Modern Medicinal Chemists can All Agree Will Not Be CNS Active

98% of potential therapeutics are unable to cross the BBB, yet…



Solving problems in drug invention is very expensive, so DO NOT make stuff a problem to be solved until you know it is a problem that needs to be solved

Δ^1–Tetrahydrocannabinol (Δ^1–THC aka Δ^9–THC)
XLogP = 6.47
Protein Binding = 99%
Solubility = 3μg/mL
Half-life = days
<1% of THC administered IV is found in the brain at the time of peak psycho-activity
Bioavailability following the smoking route was reported as 2−56%(!!); oral 10-20%
4/20 is the only number that really matters for THC

Breaking SO many drug discovery rules. Must just be a placebo effect, right?

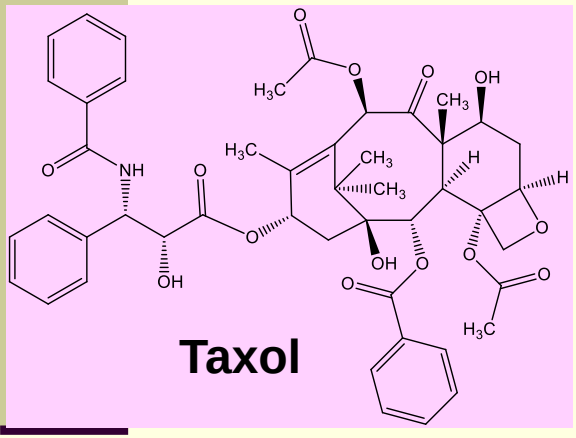
The Cancer Phenotype is the Natural Home for Irreversible Binding Drugs and Dirty Multitargeted Drugs

- Between 1000-10,000+ Mutations have been Implicated in Contributing to a Single Human Cancer – ***cancer is one hot molecular biology mess***
- A recent breast cancer study demonstrated that in ***100 patients' tumors, a high genomic diversity rate of 73% was seen, including 7200point mutations, 280 indels, 1700 homozygous deletions and 1750 deletions***. In a separate study, high rates of somatic mutations (~66%) were observed to occur in separate sections across regions of a single tumor.
- Master Driver-mutations vs. benign Passenger-mutations
  - The **driver-mutations** are the underlying molecular wellspring of tumors.
  - Countless mutations arise from the general genetic instability seen in tumors. Most are **passenger-mutations**. These extraneous mutations do not appear to play a role in tumor development or maintenance, until they do.
- **"Since tumor cells are masterful survivors, capable of so many evolutionary-driven mechanisms of drug-resistance and of introducing a multitude of pro-malignancy obstacles to molecular therapeutic interventions, *it hard to imagine any lasting therapeutic advantage of single-targeted drugs for treating cancers"***

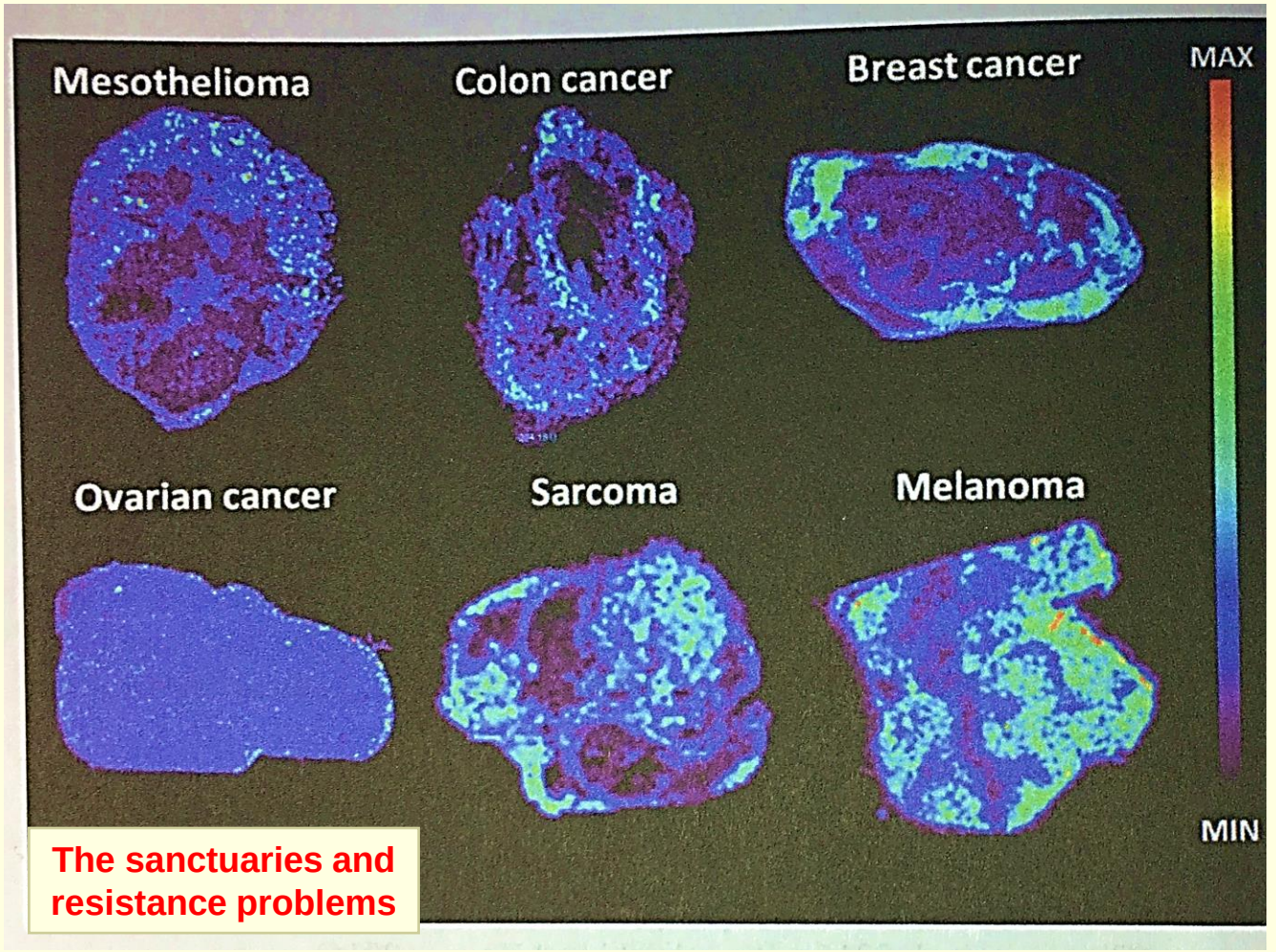
The search for selectively promiscuous drugs

Why One Cancer Drug is Efficacious in One Tumor Type or Even Just One Tumor in a Single Patient But that Drug Fails In Another Tumor Type or Even Satellite Tumors

A breast tumor IS NOT an ovarian tumor



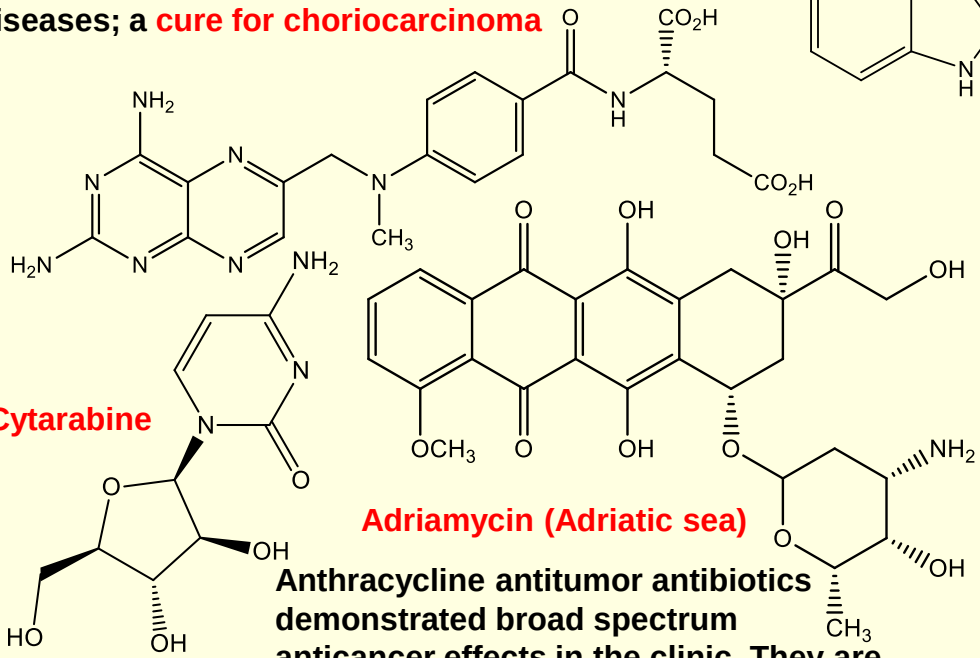
Taxol concentrations in various cancer tissues in different cancer models – light color shows high drug concentrations and darker color shows low to nonexistent drug concentrations in tissue!



Some of the High-Impact Natural Product-Based Anticancer Drugs and their MOA

1961-1981 NCI Screening Effort – 144,045 Plant Extracts and 16,000 Animal Extracts

Methotrexate- semisynthetic substrate-based inhibitor of the folic acid utilizing enzyme Dihydrofolate Reductase. It inhibits cancer cell proliferation by starving cells of the DNA building block thymidine. Discovered in 1949 and FDA allowed use in ALL in 1953. Still heavily used in cancer and autoimmune diseases; a cure for choriocarcinoma



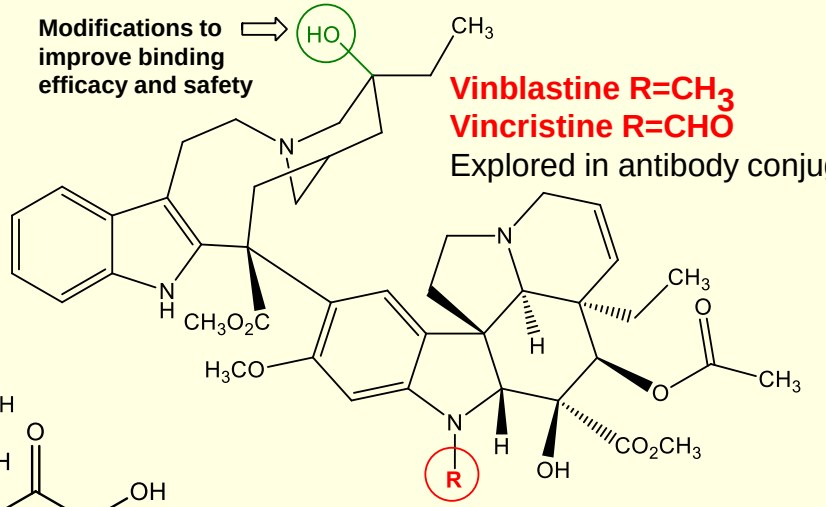
Cytarabine

Ara-C was isolated from a sponge in 1955. DNA chain terminator. High levels of clinical activity in pediatric leukemias

Adriamycin (Adriatic sea)

Anthracycline antitumor antibiotics demonstrated broad spectrum anticancer effects in the clinic. They are intercalating Topoisomerase II inhibitors that cause unrepairable double stranded breaks in DNA. Major go-to drug for many cancers
Explored in antibody conjugates

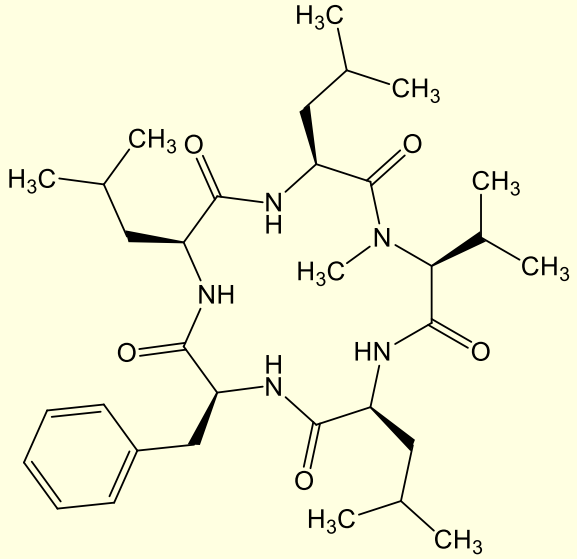
Modifications to improve binding efficacy and safety



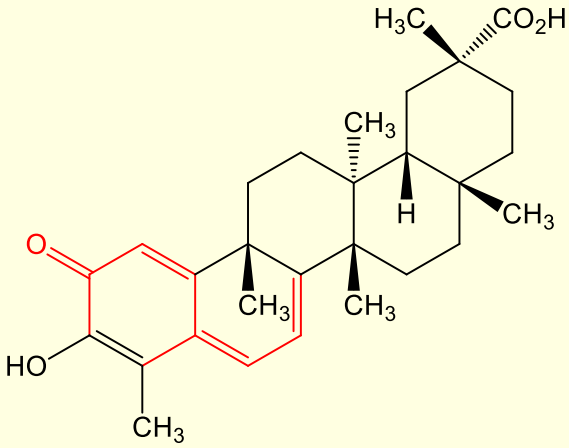
Vinblastine R=CH_3
Vincristine R=CHO
Explored in antibody conjugates

Tubulin polymerization inhibitors, the vinca alkaloids were the 1st plant-derived registered anticancer drugs. Used as a folk medicine for diabetes, they were isolated in 1959/1962 and shown to have significant antitumor activity. They were *approved for cancer therapy in 1961/1963- ONE YEAR after isolation*. They have distinct toxicity and efficacy features Vinblastine is quite toxic and effective in germ cell cancers whereas vincristine displays milder toxicities and is used in pediatric cancers and the leukemias/ lymphomas/ NSCLC. Several simple analogs of vinblastine have found wider clinical use with significantly different binding, safety and activity profiles

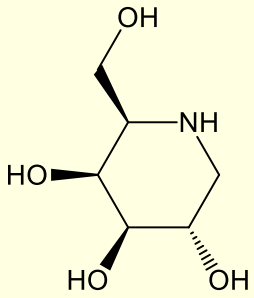
Natural Products that Disrupt Protein-Protein Binding in Hsp90 "Quality Control" Chaperon Complex



Sansalvamide-A – An allosteric inhibitor of Hsp90 which binds middle domain of Hsp90 and disrupts C-terminal binding of co-chaperon protein, Hop

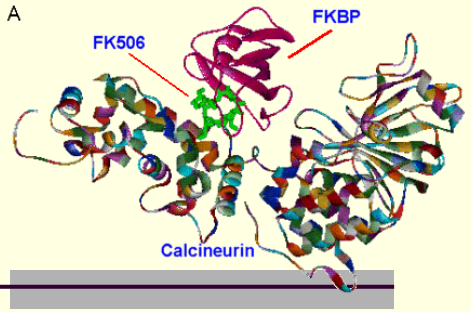


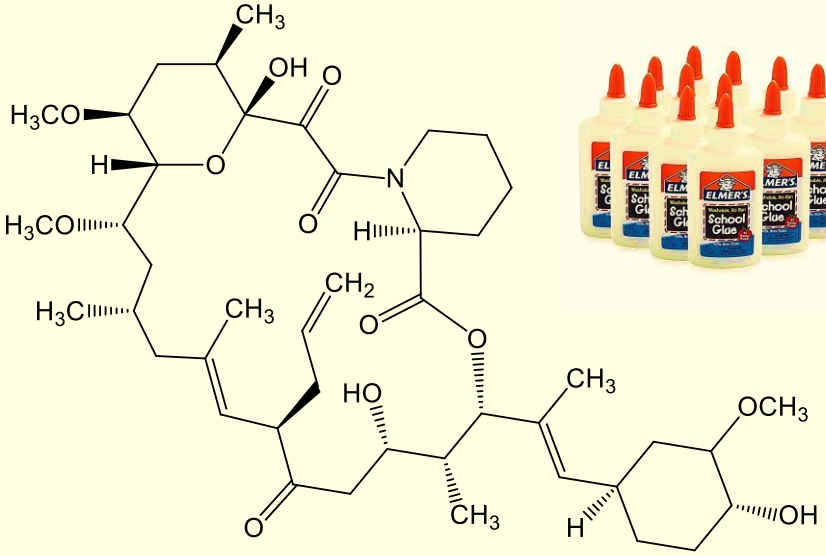
Celastrol – A Hsp90 binding molecule directly **disrupts Hsp90 binding to co-chaperons Cdc37 (covalent) and p23 (non-covalent);** HSP90 inhibitor that induces Hsp70, Hsp27 and Hsp32; also, a I-Kapa B kinase inhibitor for treating inflammation – thunder god vine root extract; potent anti-obesity activity – increases HSF-1 temperature sensor metabolism regulator, binds to Myc-Max and inhibits Myc function



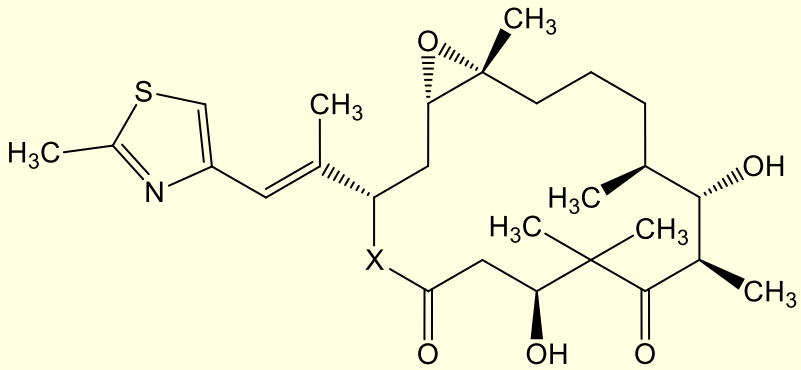
1-deoxygalactonojirimycin - Used for the long-term treatment of Fabry disease ***by shifting the folding behavior of faulty α-Galactosidase towards the proper conformation***, resulting in a functional enzyme - **pharmacological chaperone** - priced at **$315,000/y** for a very old nonproprietary simple natural product

Applications of **Molecular Glue** to Protein-Protein Interactions

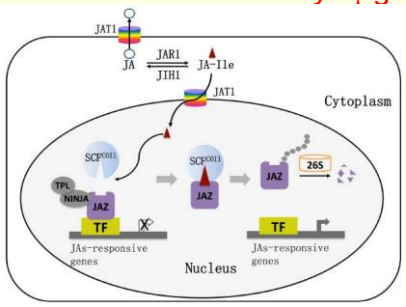




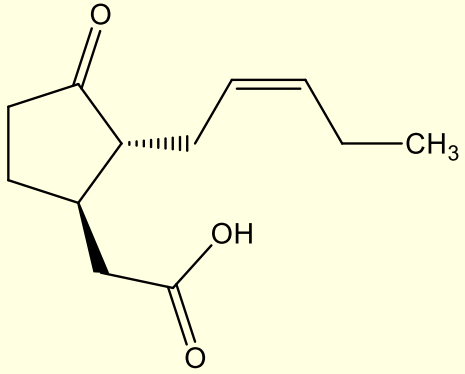
Tacrolimus opportunistically binds to a prolyl-prolyl isomerase **FK506-BP**; this drug enzyme dimer complex then opportunistically binds to and inhibits a key phosphatase, **calcineurin**, which is responsible for immune response in T-cells.
Water solubility 4μg/mL, Oral BA 4-89%



Epothilone B (X=O) was discovered in 93 as a **fungicide,** subsequently is was shown to display the microtubule stabilization MOA as taxol but with improved solubility, higher potency and activity against taxol resistant cancers. Analog **Ixabepilone** (X=NH) displayed better metabolic stability and was approved by the FDA in 2007 for treating advanced Brest cancer. Numerous me-too analogs with improved features are in development

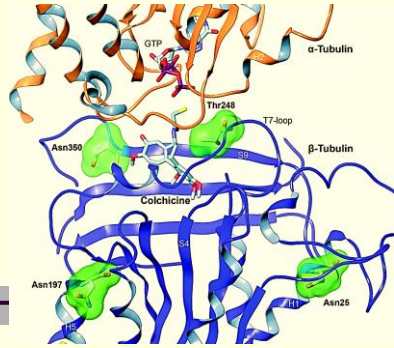


Jasmonic acid a plant hormone that regulates the defense stress response to herbivores, insects and fungi. It functions by complexing with a **plant E3-type ligase SCF** (Skp1, Cullin and F-box proteins) creating a new recruitment surface target substrate, **JAZ**, for ubiquitination and subsequent proteasome degradation – **a natural small molecular glue-like protein degrader**

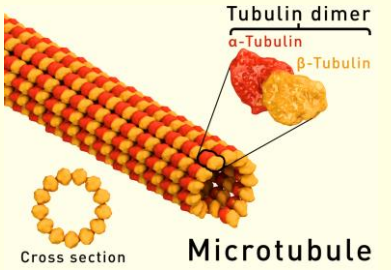


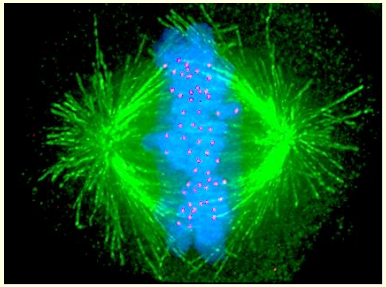
Microtubules: The Emperor of Non-DNA Cytotoxic Molecular Targets

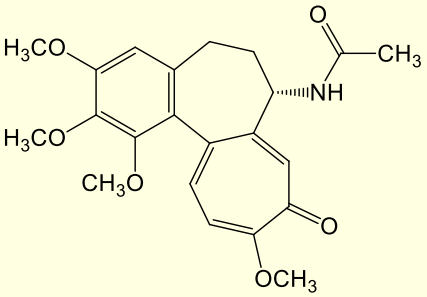
The Spindle Poisons



- α and β–tubulin proteins dimerized and then reversibly polymerize to extended filamentous tubular microtubules which in turn are responsible for multiple crucial aspects of cell morphology, a key one being the formation mitotic spindle in cell division
- This process of microtubule assembly and disassembly **is driven by GTP (polymer) to GDP (dimer) hydrolysis** (called ***tread milling - forming at one end and dissolving at the other***)
- Multiple important antitumor cytotoxic drugs act on tubulin-microtubule spindle equilibrium which is much more dynamic than cytoskeletal assembly-disassembly which explains why dividing cells are much more sensitive to these agents
- There are two classes of spindle poison drugs **1) those that inhibit microtubule assembly**, AKA microtubule destabilizing agents, and **2) those that inhibit microtubule disassembly**, AKA microtubule stabilizing agents. These effects lead to ***Mitotic Catastrophe***
- The active agent in **autumn crocus**, the traditional botanical medicine for treating gout and rheumatism (Ebers Papyrus *circa* 1500 BCE), is the alkaloid colchicine.
- **Colchicine** (**FDA approved in 2009**) was the molecular probe molecule that played a key role in the 1930s for investigating microtubule molecular biology and its relation to the spindle poison anticancer effects of this natural product
- **In clinical trials, it proved too toxic for use in cancer therapy, it is useful for treating gout, pseudo-gout and other inflammatory conditions**
- Colchicine is one of a large number of microtubule destabilizing agents that include the vinca alkaloids, cryptophycin-1, combretastsatins, steganacin, numerous synthetic compounds like agrichemical fungicides like nocodazole and thiabendazole, and maytansine and dolastatin in the new targeted anticancer antibody drug conjugates
- HDAC6 selectively removes acetyl groups from tubulin – the key MOA for HDAC inhibitors?





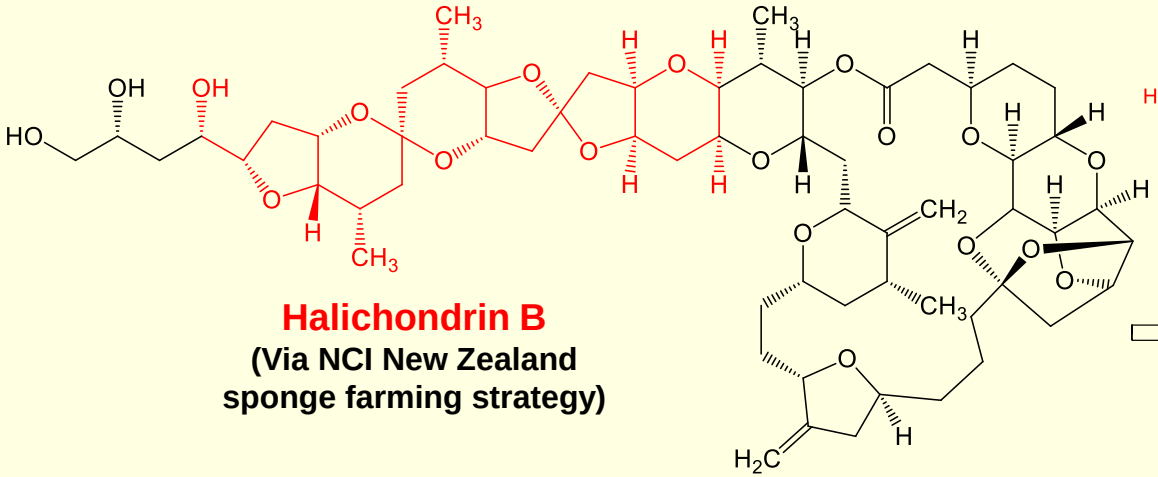


Colchicine – gout drug

Eribulin – A Chemical Tour de Force in Pharmacophore-Driven Medicinal Chemistry

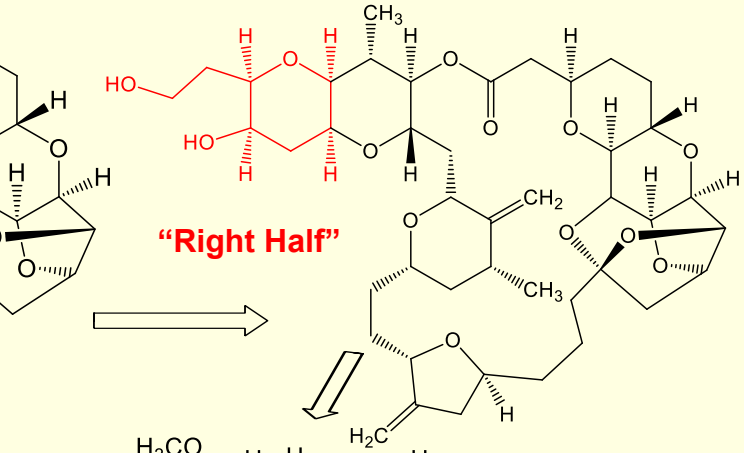
From the Sponge Mashers to the Medchem Synthesis Jockeys

NO Natural Product Drug Candidate is Out of Reach of the Synthesis Manufacturing Jockeys

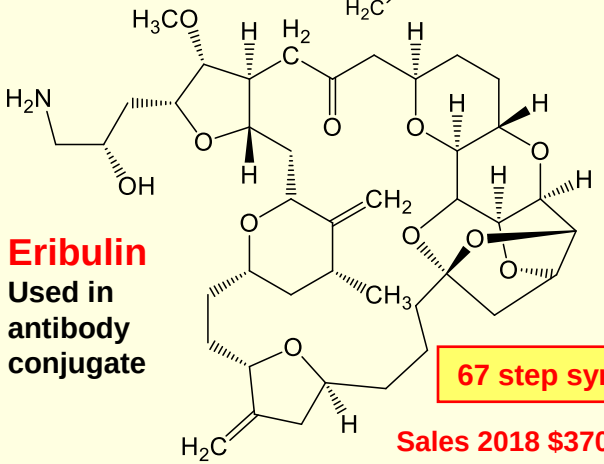


Halichondrin B
(Via NCI New Zealand sponge farming strategy)

"Right Half"



Halichondrin B, a highly complex natural product isolated in the 80s from a western Pacific marine sponge (600kg) that displayed exceedingly potent cellular antiproliferative activity. It is unique mitotic inhibitor and appears to reduce microtubular mass by inducing nonproductive tubulin aggregates. Halichondrin was highly active in a number of xenograft models. As part of a total synthesis program to supply 10gm of material for clinical development (**selected by NCI in 1992**), multiple intermediates were prepared and bioassayed for cancer cell cytotoxicity. Total commercial needs were estimated to be 1-5kg/y. The **"Right Half" intermediate** proved highly active, was shown to target tubulin via affinitive chromatography, microtubule formation and spindle formation. This key intermediate was the starting point for SAR exploration requiring very demanding chemical synthesis **(>200 analogs) efforts ultimately yielding the drug candidate, erbulin. Erbulin displayed significant in vivo antitumor activity in multiple xenograft models at doses in the 0.05-1mg/kg range.**



Eribulin
Used in antibody conjugate

67 step synthesis

Sales 2018 $370 million

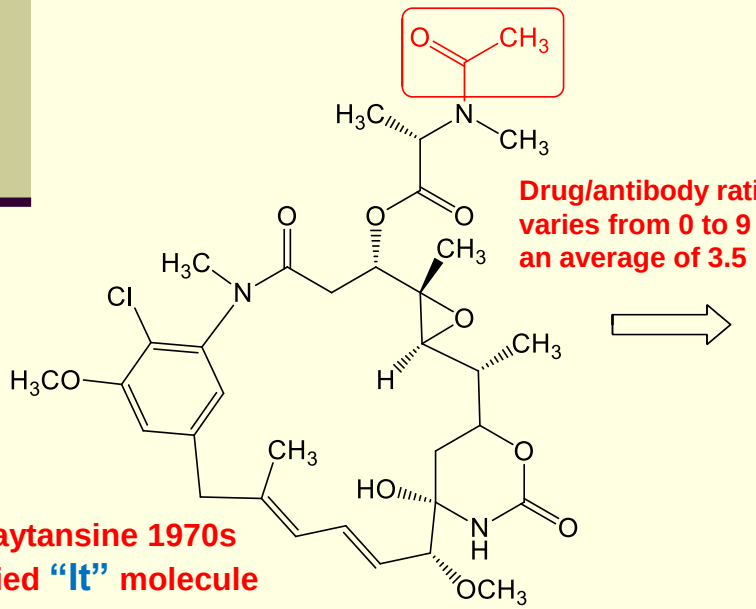
Halaven (**Eribulin**) was approved by the FDA in **2010**, to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease
Another modern endorsement for spindle poisons

The Resurrection of Maytansine

Salvation Came with the Arrival of the Magic Bullet-The Antibodies

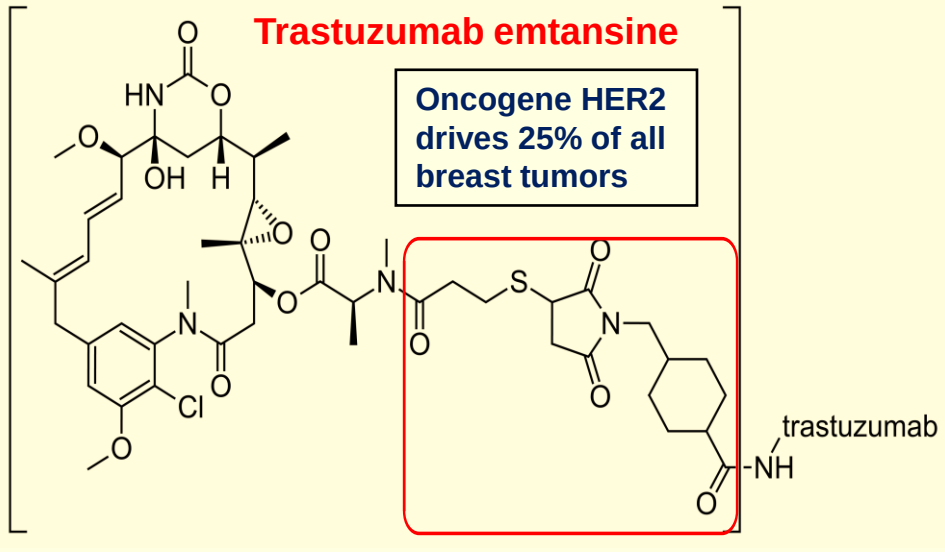
(The 1st Anticancer Antibody/Drug Conjugate was to Methotrexate in 1958)

- Maytansine is one of a number of extraordinarily potent (25μM/kg) cytotoxic macrolactams isolated was originally isolated from the Ethiopian shrub Maytenus serrata by Kupchan in 1972 during the large NCI natural product screening project of that era (**initial collection in 1961**). Its activity (T/C survival values of 220%) multiple animal cancer models generated considerable excitement in the late 70s. Clinically tested in 800 patients/35 tumors showed marginal activity poor safety
- NCI initiated clinical trials demonstrated an unacceptable safety to benefit risk profile and its development was abandoned (1980s). **However great anticancer drugs never die, they just wait on the shelf for the world to change, and it did**
- As with many highly potent cytotoxic natural product, maytansine targets microtubulin assembly, specifically be binding at the vinca alkaloid binding site – it is a great spindle poison
- **Then maytansine was reborn as a validated antibody (Herceptin)-cytotoxic conjugate - Kadcyta**
- A clinical trial of women with advanced HER2 positive breast cancer who were already **resistant to trastuzumab** alone, **improved survival by 5.8 months** compared to the combination of lapatinib and capecitabine. However only 5% of the conjugate is internalized. Based on that trial, the **FDA approved marketing in 2013 - 52 years after this story began!!**



Drug/antibody ratio varies from 0 to 9 with an average of 3.5

Maytansine 1970s storied "It" molecule

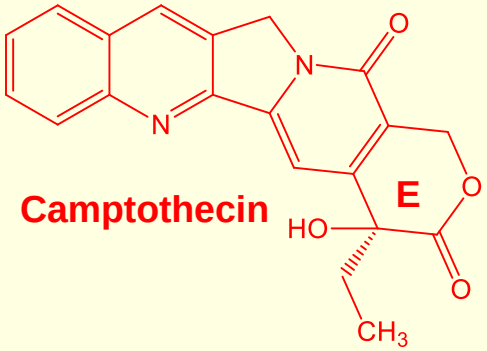


Chinese Medicinal: Camptothecin

The Shooting Star that Flamed Out and then Sparkled Again During My Professional Lifetime

Or Why ME-TOO Drug Invention Programs are so Important

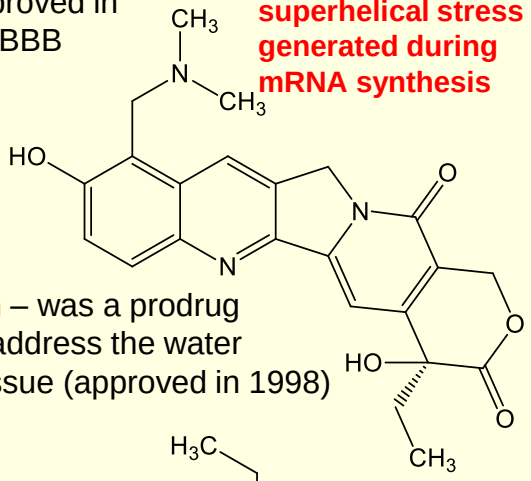
Camptothecin – traditional Chinese botanical medicine for cancer (maybe). Isolated in 1966 but proved to be too insoluble and toxic and **fell out of development until its MOA was demonstrated to involve topoisomerase I inhibition** (trapping cleavable complex) which validated Topo I as a target and would drive the hunt for safer, water soluble analogs



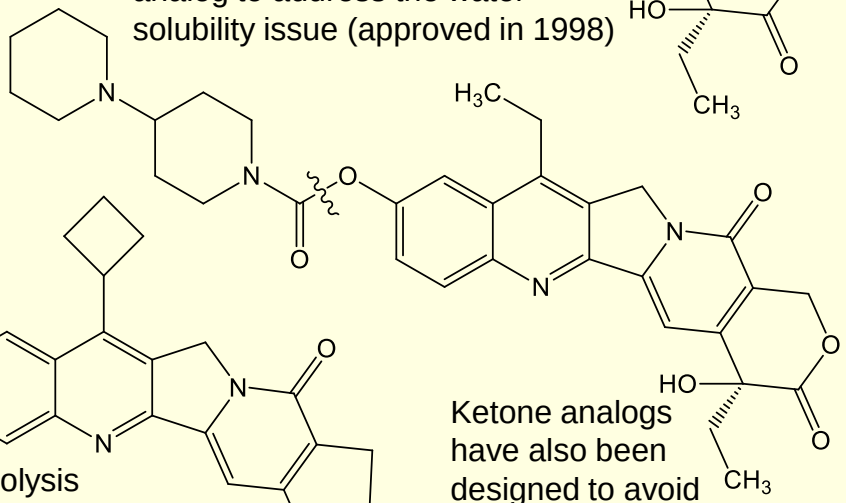
The **Camptothecin** lactone ring (**E**) is required for Topo I activity These drugs are **rapidly deactivated by hydrolysis of the E ring lactone in humans** which is effectively taken out of play upon strongly binding to albumin. The lactone reforms in acidic urine in the bladder resulting in high local bladder toxicity. Analogs explored in antibody conjugates

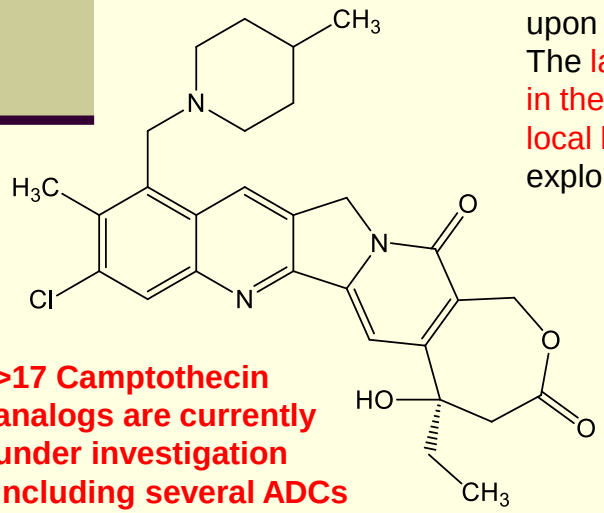
Topotecan – was the 1st analog to address the water solubility issue (approved in 1996), crosses the BBB

Topoisomerases are involved in relaxing superhelical stress generated during mRNA synthesis



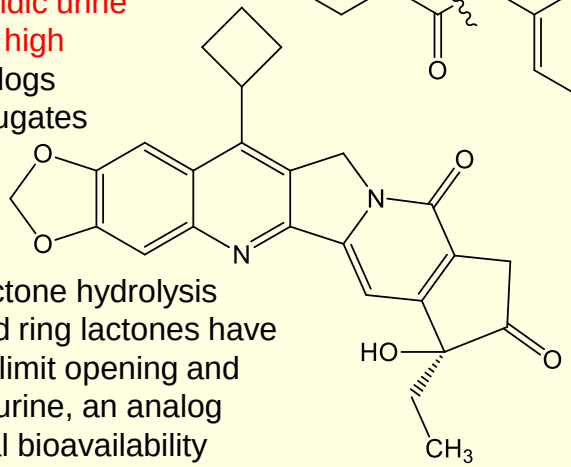
Irinotecan – was a prodrug analog to address the water solubility issue (approved in 1998)





>17 Camptothecin analogs are currently under investigation including several ADCs

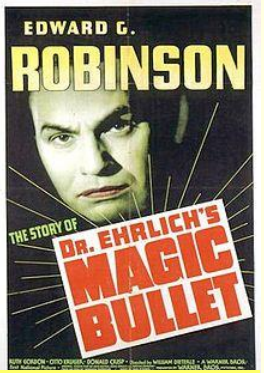
To address the lactone hydrolysis issue 7-membered ring lactones have been designed to limit opening and inhibit recloser in urine, an analog showed ~85% oral bioavailability



Ketone analogs have also been designed to avoid the lactone opening problem altogether

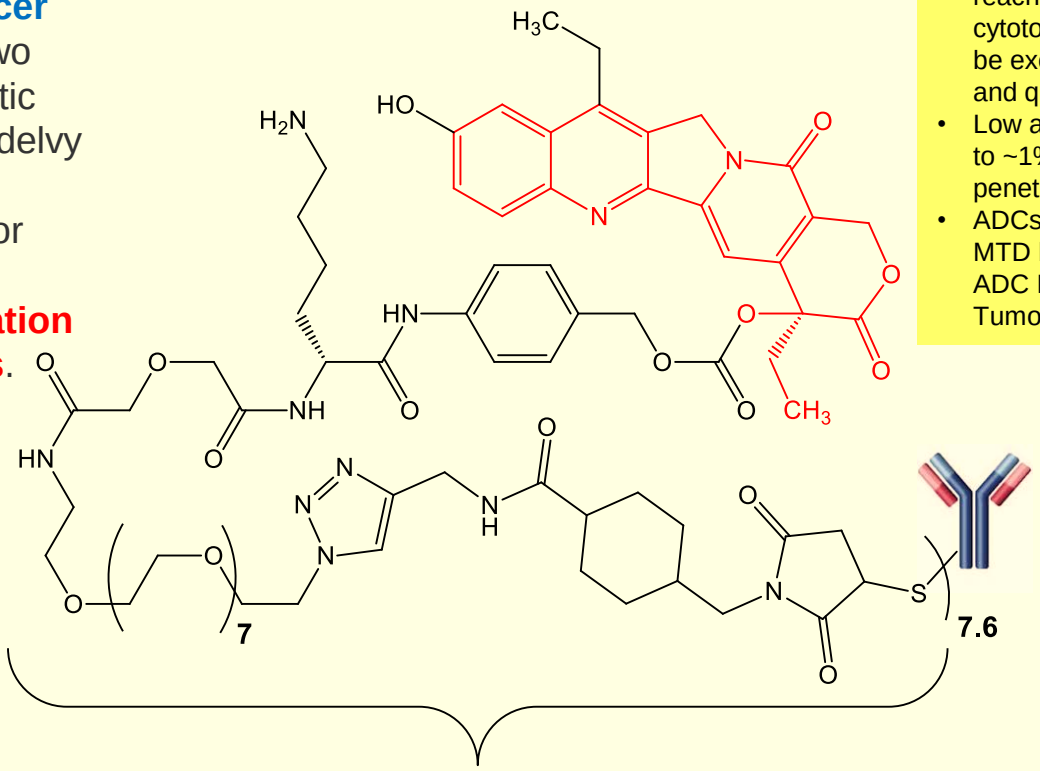
Trodelvy: The 21 Billion Dollar Molecule

The Evolving Economics of the Drug Invention Business Model



FDA approved Trodelvy based on the results of a clinical trial of 108 patients with **metastatic triple-negative breast cancer** who had received at least two prior treatments for metastatic disease. The efficacy of Trodelvy was based on the overall response rate (ORR) – tumor shrinkage. **The ORR was 33.3%, with a median duration of response of 7.7 months**.

Potent **Camptothecin** Analog



ADC observations

- >90% of the ADC never reaches the tumor so cytotoxin payloads must be exceedingly potent and quite toxic
- Low antigen counts lead to ~1% of the ADC penetrating the tumor
- ADCs MUST be Dosed at MTD because <1% of an ADC Localizes to the Tumor

Humanized monoclonal antibody against tumor-associated cal cium signal transducer 2

American Cyanamid, a major global pharmaceutical, vaccine, branded consumer health and beauty products and agrichemical manufacturer and inventor with factories, research campuses, corporate headquarters, sales and marketing was sold for **$10B** at a premium in 1995

Exotic Proprietary linker (ratio of warheads to antibody: ~7.6 to 1)

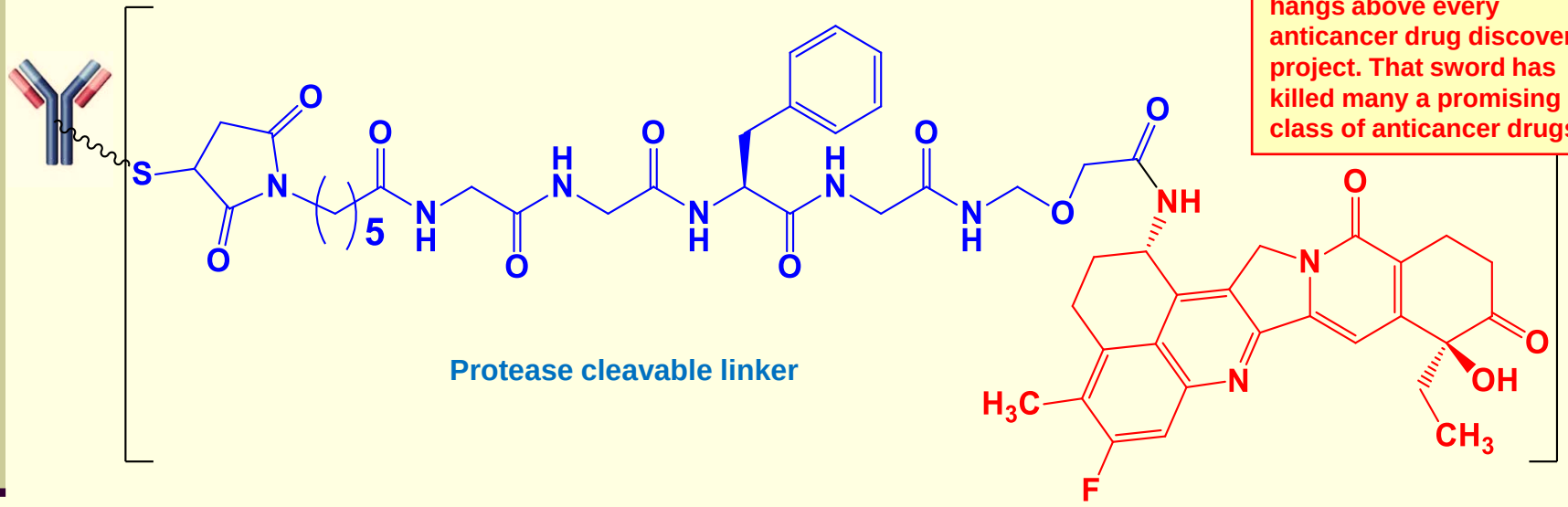
$16,096 per 21-day cycle for a 70-kg person

The Multi-Billion Dollar Wonder that is a Me-Too Antibody Drug Conjugate

Enhertu (**fam-trastuzumab-deruxtecan**-nxki)

HER-2 Antibody Address

In oncology, the narrow Therapeutic Index (TI) problem is the sword that hangs above every anticancer drug discovery project. That sword has killed many a promising class of anticancer drugs



Protease cleavable linker

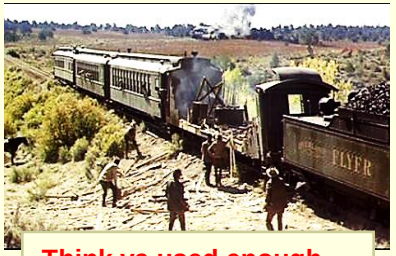
7.7

Another **HER-2 Antibody Address** and a **Me-Too Camptothecin** analog: FDA approved trastuzumab deruxtecan based oh one clinical trial enrolling 184 female participants with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies in the metastatic setting. The **overall response rate was 60.3%,** with a **median duration of response of 14.8 months** all for a per-patient cost of around **$13,300 per month – estimated peak sales $2.5 billion**

Camptothecin analog **exatecan** targeting topoisomerase 1

The ASCO Headlines:** **trastuzumab deruxtecan reduced the risk of disease progression or death by 50% compared with chemotherapy** **for human epidermal growth factor receptor-2 (HER2)–low patients with both hormone receptor (HR)–positive and HR-negative disease.

So Much Slicker than Bind and Alkylate: The Proper Way to Kill a Target Enzyme - **A Suicide Substrate**

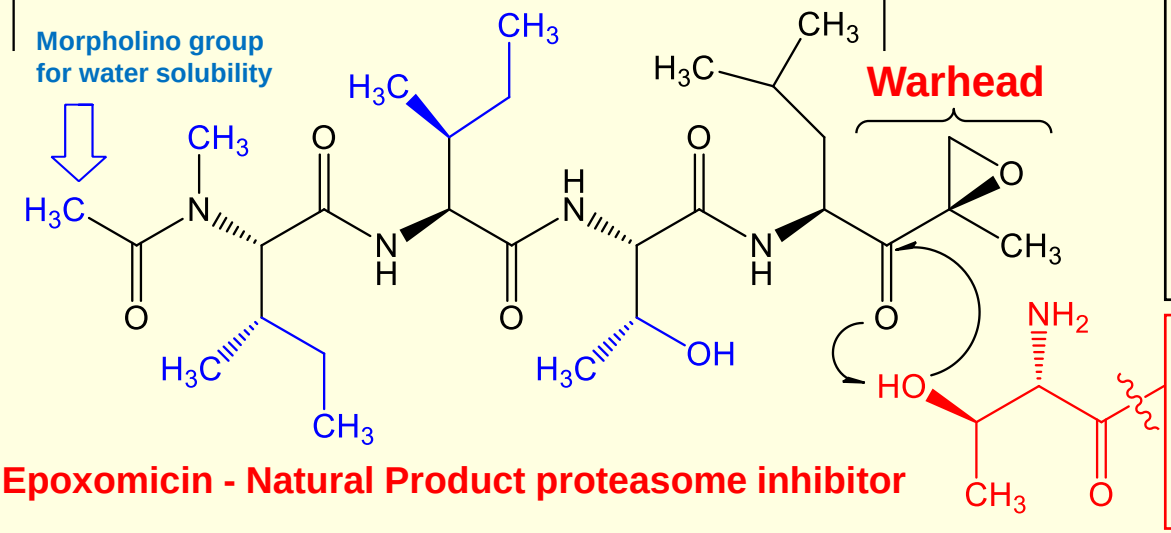


Think ya used enough dynamite there, Butch?

Address

Morpholino group for water solubility

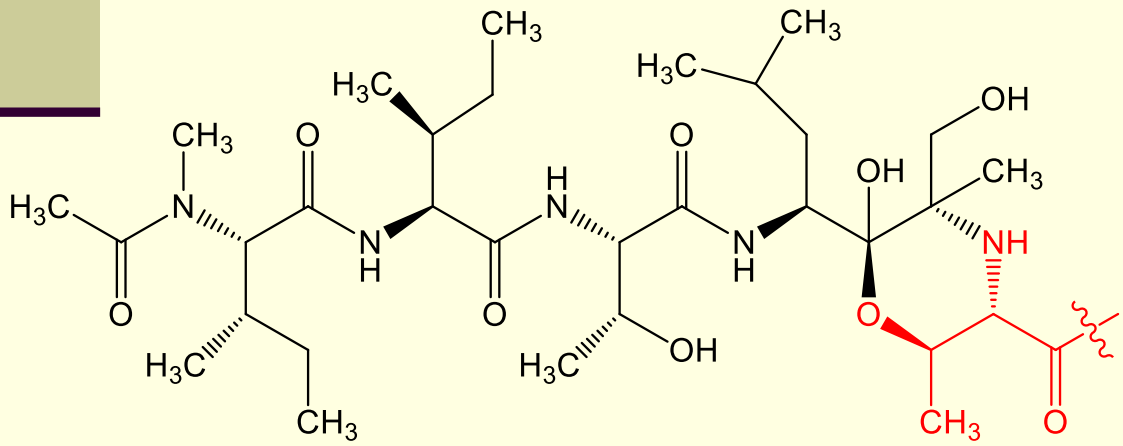
Warhead



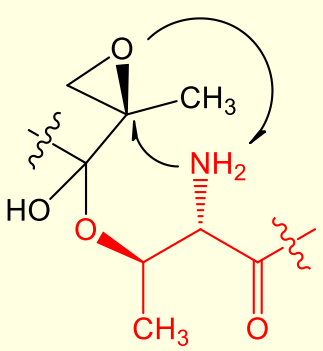
Epoxomicin - Natural Product proteasome inhibitor

Epoxomicin was morphed into registered anticancer proteasome inhibitor drug, Carfilzomib ($1.3B), by using classic peptide sidechain substitution medicinal chemistry tactics

Proteasome active site – a protein *InSinkErator* - much too important to be a viable drug target – inhibitors will be too toxic to be useful drugs

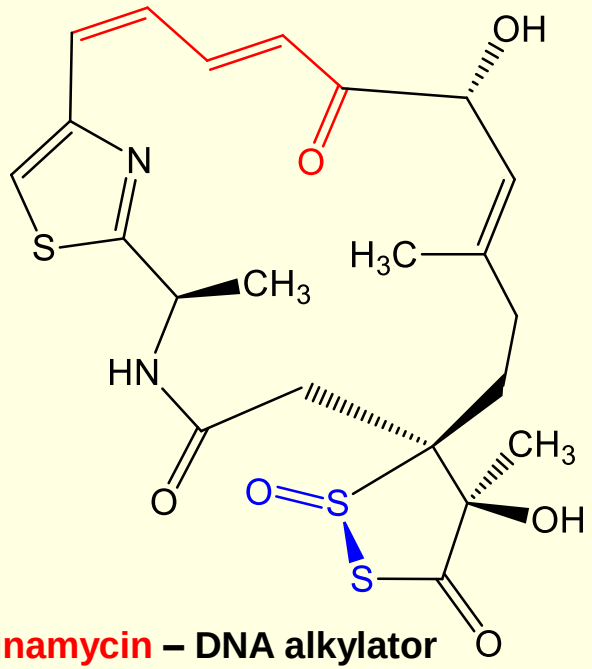


Dead proteasome-epoxomicin covalent adduct

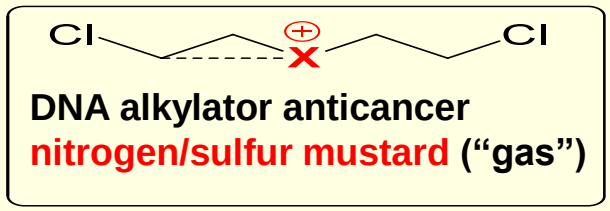


Enzyme-lethal irreversible covalent bond formation

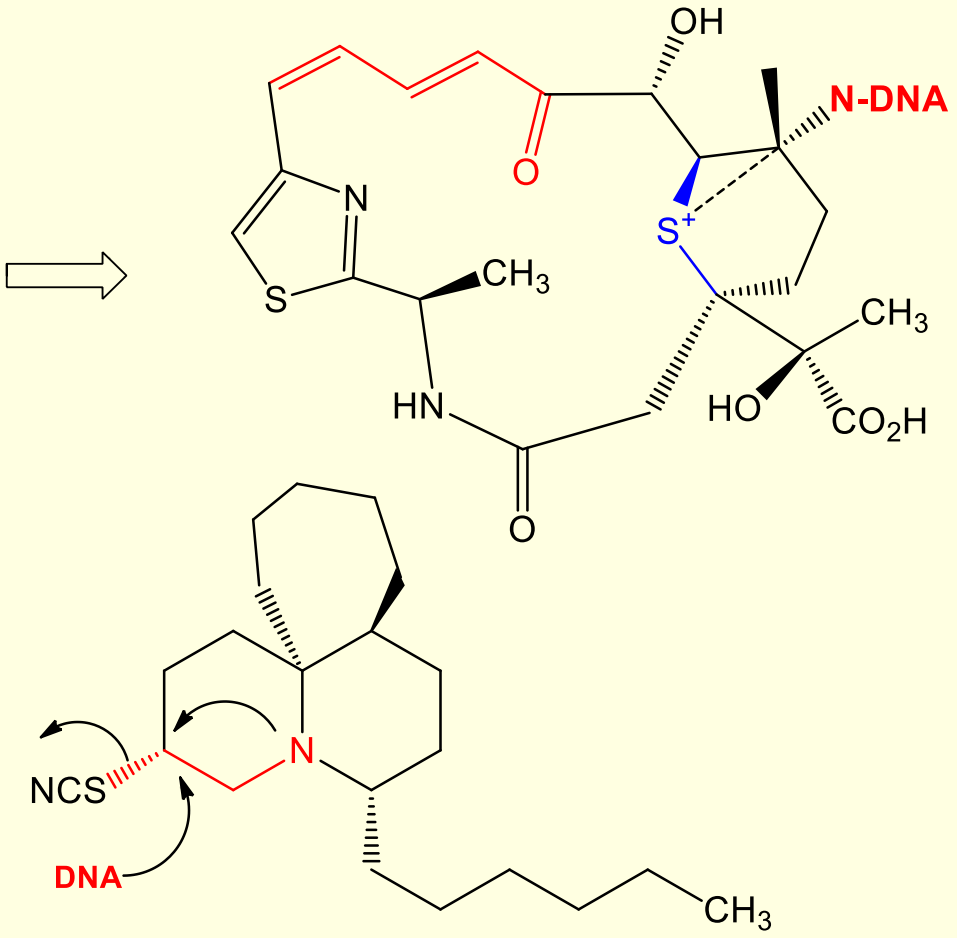
Natural Mustard "Gas" Anti-DNA Anticancer Agents



Leinamycin – DNA alkylator potent antitumor natural product sulfur mustard mimic



DNA alkylator anticancer nitrogen/sulfur mustard ("gas")



Fasicularin – DNA alkylator antitumor natural product nitrogen mustard mimic

Artificial Transcription Factor Type Inhibitors?

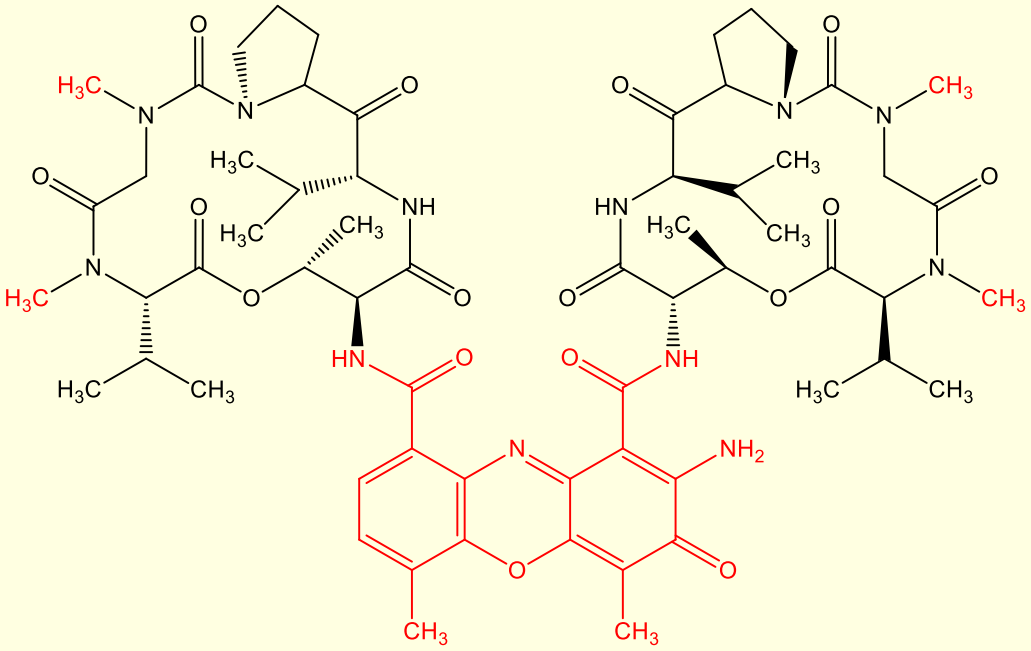
The Amazing Molecules that Cross Cellular and Nuclear Membranes when They Should Not

Perfection is the Enemy of Good Enough to Get the Job Done

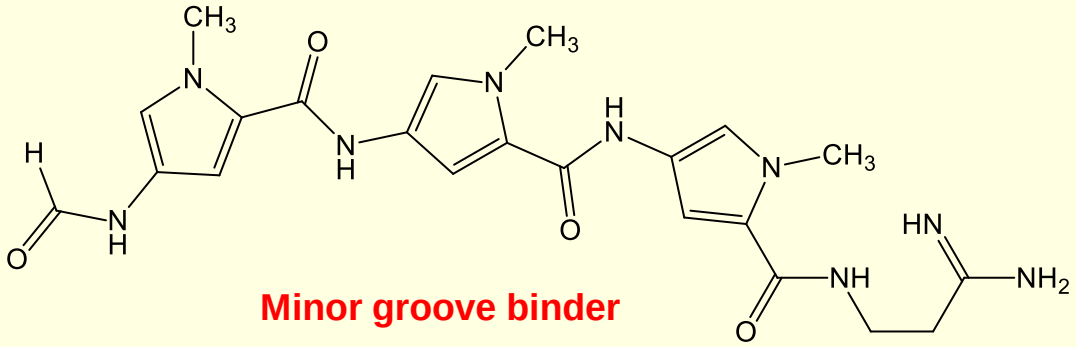
Actinomycin D was discovered in**1954**. It is a **DNA intercalating, minor groove binder** – **mini repressor**? Approved 1964 by FDA for a number of cancers including Wilms' tumors, lymphomas, Ewing sarcomas and genital cancers.

Numerous natural products also interact with RNAs specifically multiple classes of antibiotics

A hybrid **intercalator-groove binder**



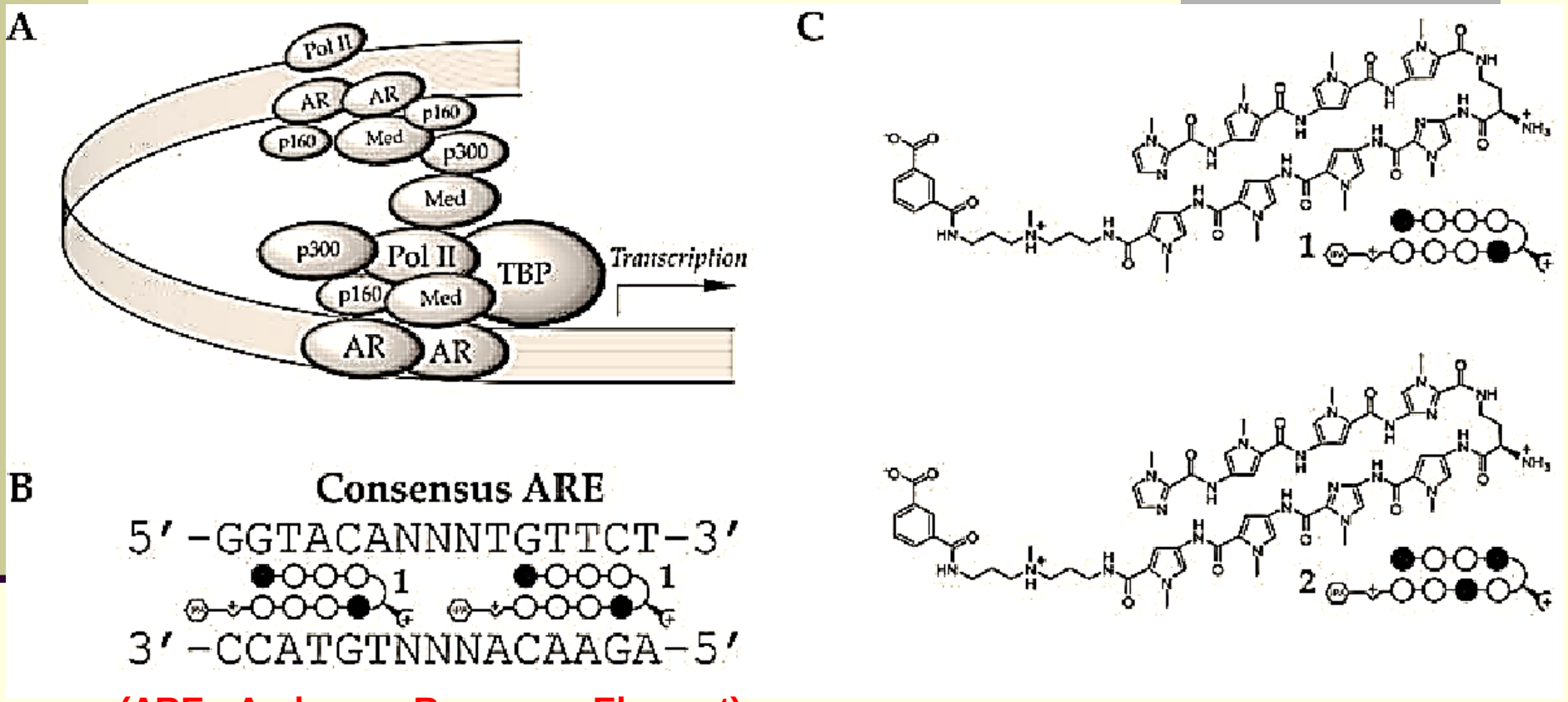
Distamycin is a pyrrole-amidine antibiotic which acts as a **minor groove binder** and **inhibits the transcription** and increases the activity of the topoisomerase II. Distamycin **prefers AT-rich DNA-sequences** and tetrades of $[TGGGGT]_4$



Minor groove binder

Distamycin-Inspired Transcriptional Repressor Molecule

Artificial Androgen Receptor Dimer – DNA Palindrome Binding Site Inhibitor with In Vivo Activity



(ARE - Androgen Response Element)

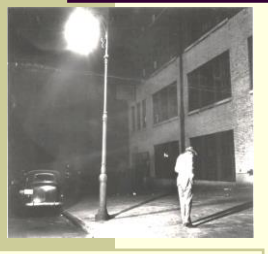
#1 was active in 3 prostate cell lines LNCaP (IC_{50} = 2μM), VCaP, and LREX'.
Xenograft (VCaP) studies in prostate cancer: s.c. dosing, 3X per week showed dose dependent 70% reduction in tumor growth at 5mg/kg w/o toxicity

Antitumor Terpenoids:

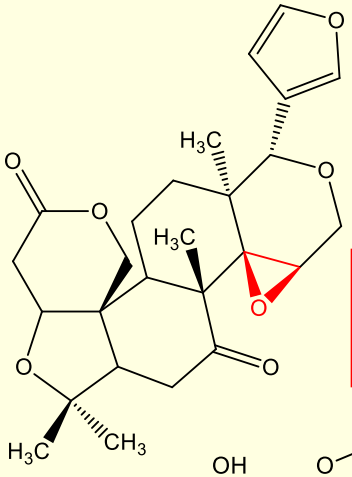
MOA Promiscuity and Unknown Molecular Targets

Drug Polypharmacology at Its Finest – The **Network Poisons**

We Search Where There is Light – Goethe



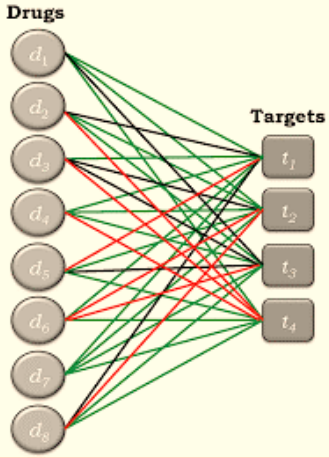
An exercise in searching under the lamppost



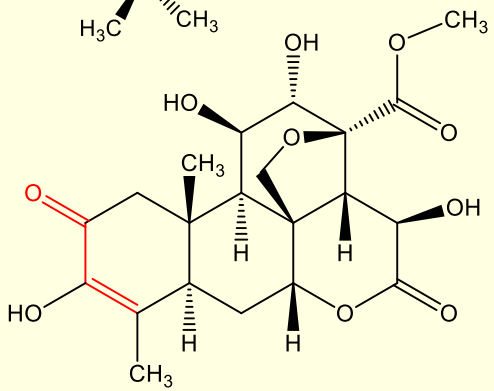
Limonin

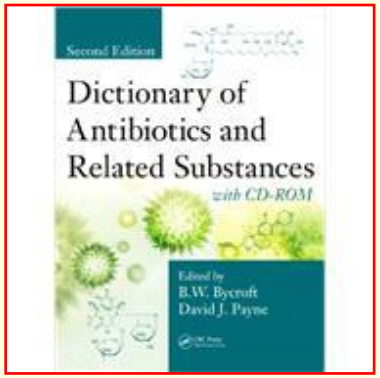
Inhibits colon adeno-carcinoma cells which is associated with decreased levels of Bcl-2 increased levels of cytoplastic Ca^{2+} with a fall in mitochondria membrane potential, release of cytochrome C and activation of caspase 3 (antiparasitic activity)

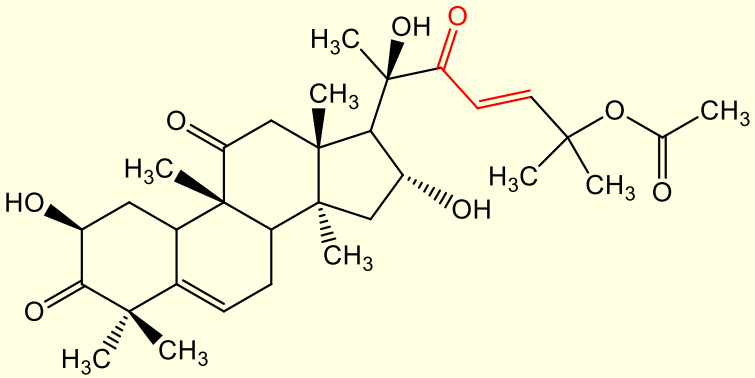
For malignant, infectious and psychiatric diseases perhaps promiscuous network poisons MOAs will yield more robust PROTAC pharmacology?



Biological Networks possess emergent properties making predicting the output from the sum of the parts (reductionism) impossible







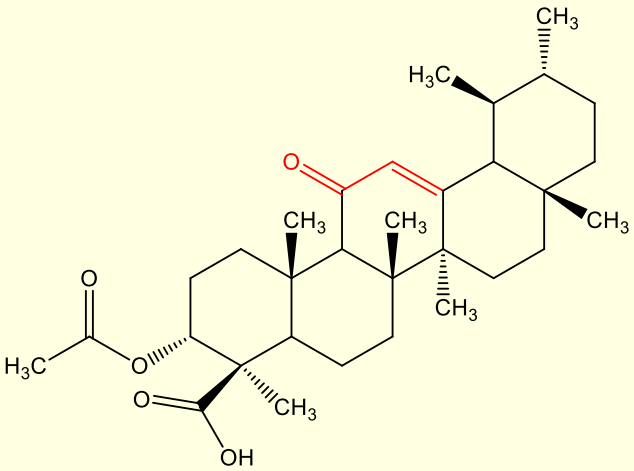
Bruceolide(Quassinoids)

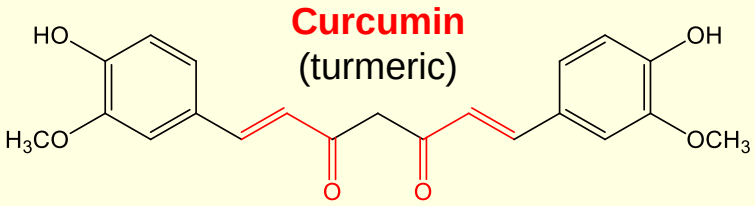
T/C at 4mg/kg 147% - P2 trials; inhibits protein synthesis via impairment of peptidyltransferase and inhibits DNA and RNA synthesis via phosphorobosyl pyrophosphate aminotransferase; active in multiple cancer cell-lines; In vivo antimalarial activity

Cucurbitacin B

Induces STAT3/inhibits phosphorylation, inhibits the Raf-MAPK pathway; reduces cMyc and telomerase activity; inhibits cyclin D1, CDK1, c-Raf activation and an increase in ERK phosphorylation; reduced levels of cyclin B and cdc25C, activates caspases 3, 7, 8,and 9; elevates of ROS levels inducing actin aggregation; active in multiple cancer cell-lines (Hsp90 target?)

Boswellic Acid – A Typical Natural Product Scaffold with a Zillion MOAs Impacting Cancer





Curcumin
(turmeric)

Beware of the Old Adage: "Where there are many cures, there are no cures"

Acetyl-11-keto-β-boswellic acid - is a Drug In Search Of a Disease

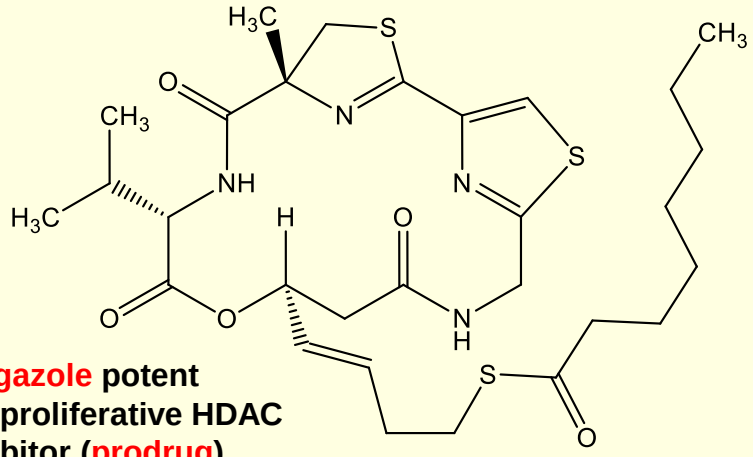
Induces apoptosis in HL-60 and CCRF-CMC cell-lines down stream of ceramide-dependent receptor (Fas); repressed TOPO I and II expression; boosted free cytoplastic Ca^{2+} levels from endoplasmic reticulum leakage and hence MAPK p38 activation which in turn results in CHOP induction, superoxide production and increased levels of ROS. Repressed growth of LNCaP and PC-3 cells with activation of pro-apoptotic JNK via free Ca2+ and CHOP inducing transcription of the death receptor DR5 with subsequence of caspases 8 and 3 and cleavage of PARP; Multiple myeloma became apoptotic due to inhibition of JAK2 with inactivation of STAT3 and subsequent reduced transcription of Bcl-2, Bcl-xL, Mcl-1 and cyclin D1

For promiscuous bioactive molecules, it is always about identifying just the right clinical indication

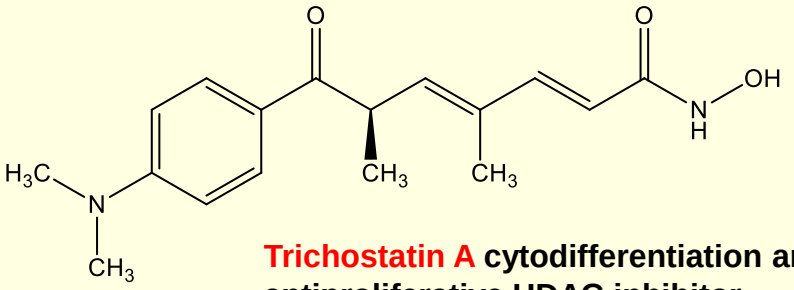
Natural Product HDAC Inhibitors

Stop the Program! – ***Prolifix SAB "Modulating Gene Expression with such a Blunt Instrument as a HDAC Inhibitor was Bound to be Grossly Toxic"***

Too brilliant by a Half? Or just Missing the Future by Looking in the Rearview Mirror?

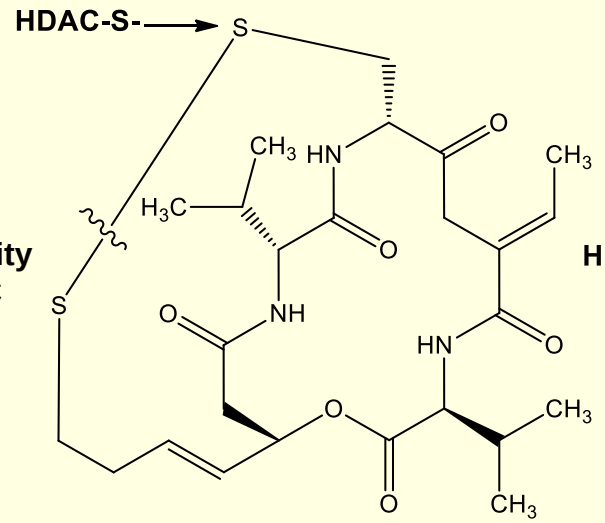


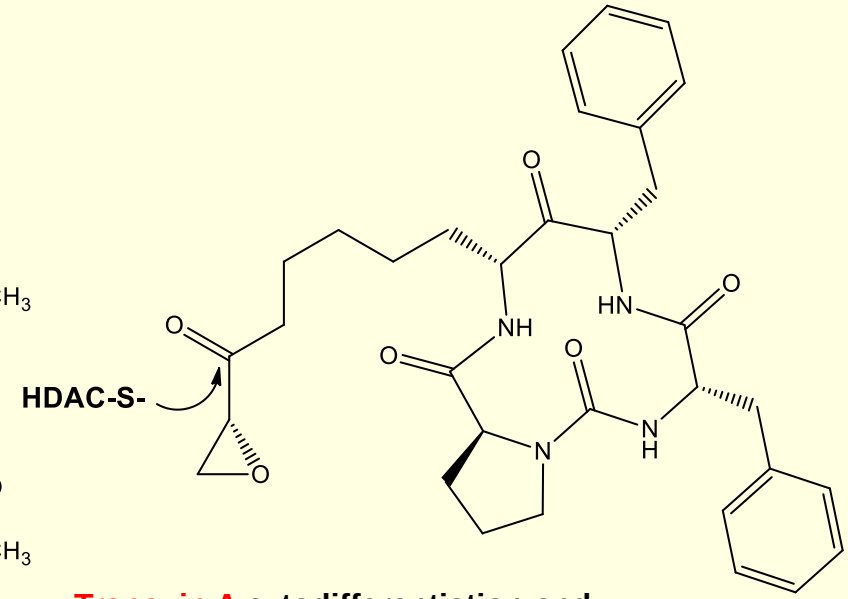
Largazole potent antiproliferative HDAC inhibitor (prodrug)



Trichostatin A cytodifferentiation and antiproliferative HDAC inhibitor

Romidepsin FDA approved for cutaneous T-cell lymphoma in 2009. Displays herbicidal activity by interaction with plant HDAC





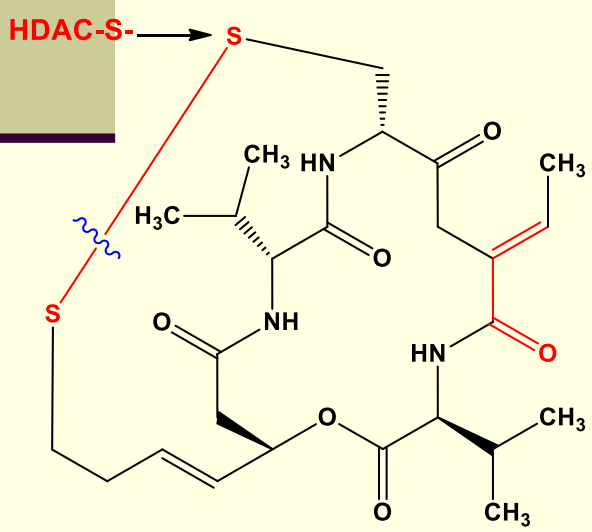
Trapoxin A cytodifferentiation and antiproliferative covalent binding HDAC inhibitor

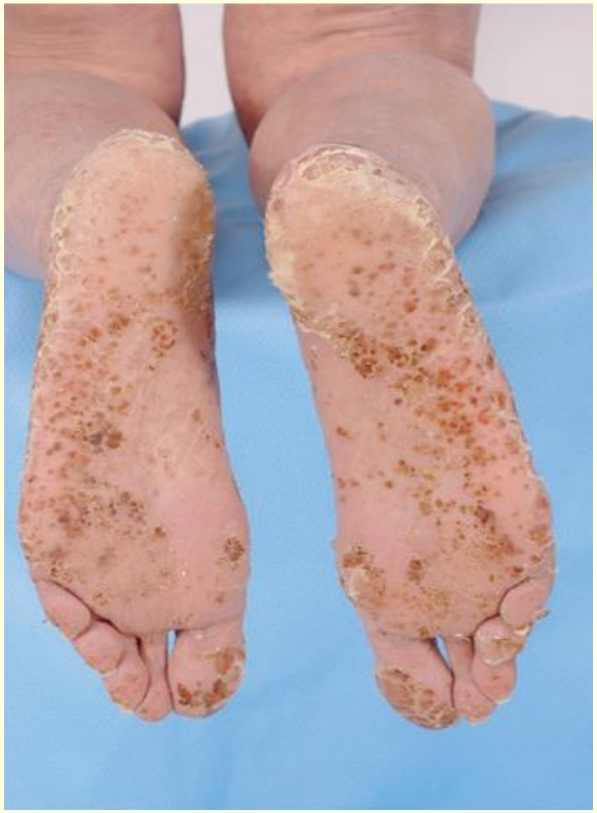
Complex Irreversible Marine Prodrug Inhibitor of HDAC with Poor Oral Bioavailability, Yet a Big Clinical Effect

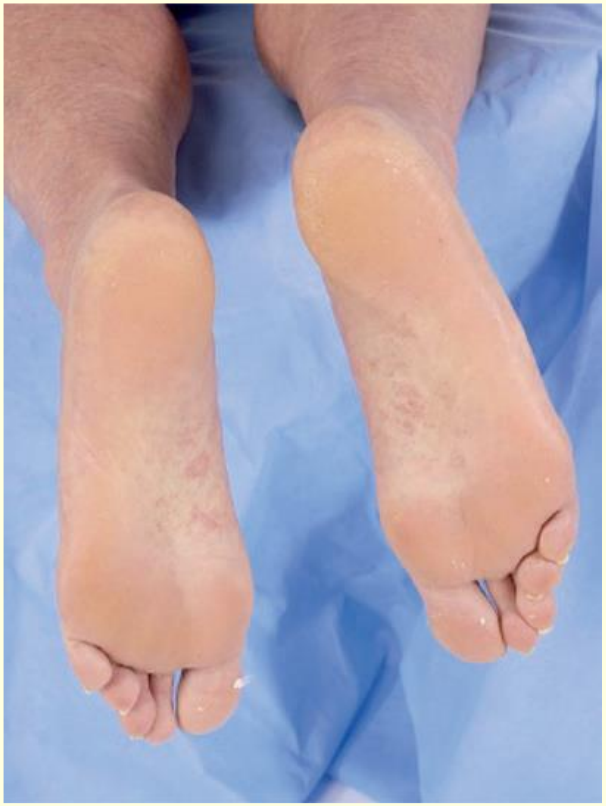
When you Don't Need a Statistician to Tell You that Your Drug Works – AKA, *the Inter-Ocular Impact Test*

Romidepsin FDA approved for cutaneous T-cell lymphoma; this Fugisawa HDAC inhibitor - stopped because of cardiotoxicity, but this was manageable with a specific schedule – Fixing a problem in the clinic not in the medicinal chemistry lab

Orally available *f* =16%
$T_{1/2}$ – 8hr



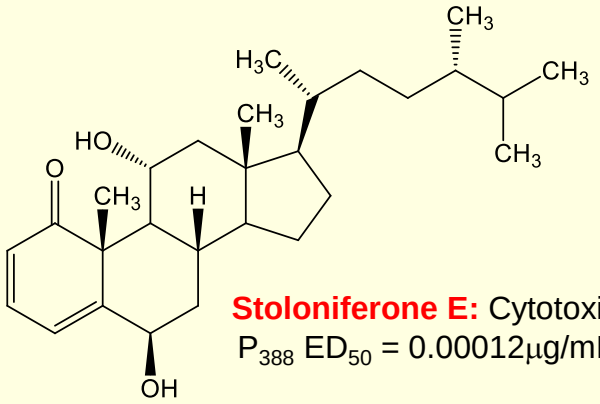




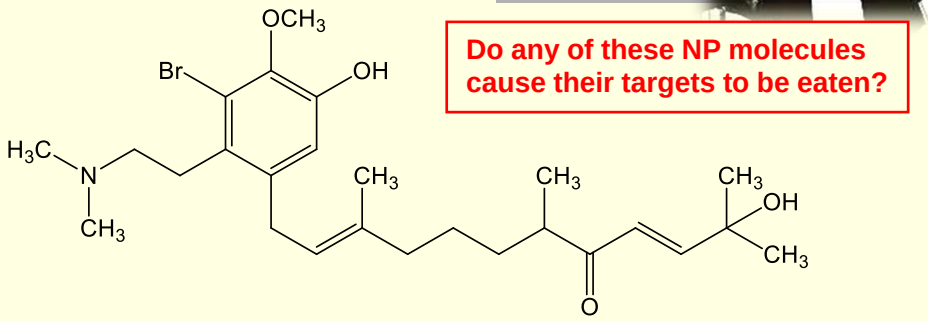
Clinical Images Obtained before and after Treatment with Romidepsin in a Patient with Cutaneous T-Cell Lymphoma (CTCL) A patient presented with CTCL lesions on the soles of his feet (left panel).After treatment with romidepsin in a clinical trial, a marked clinical response was noted, with disappearance of the plantar lesions (right panel).

Molecular Target Fishing with Marine Natural Product Baits

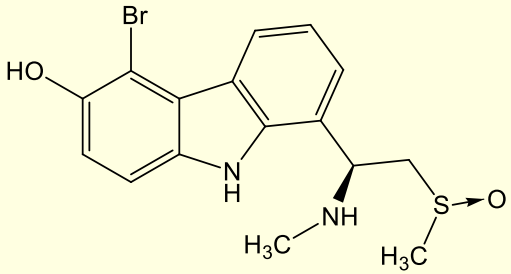
Do any of these NP molecules cause their targets to be eaten?

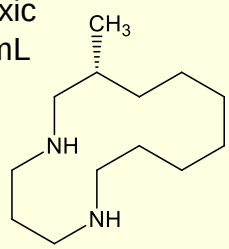


Stoloniferone E: Cytotoxic P_{388} ED_{50} = 0.00012μg/mL

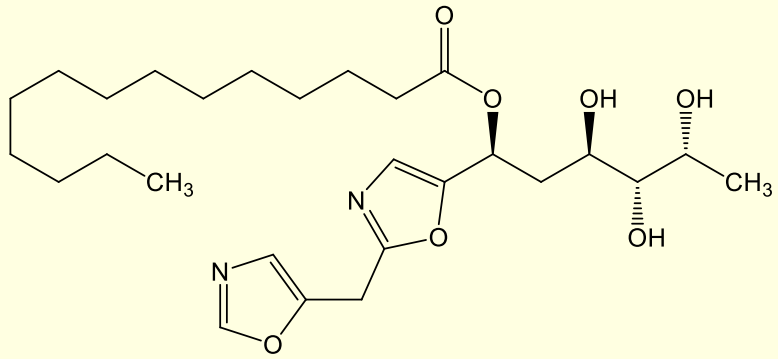


Neoplaminone: Cytotoxic HeLa-S3 IC_{50} = 0.00016ng/mL





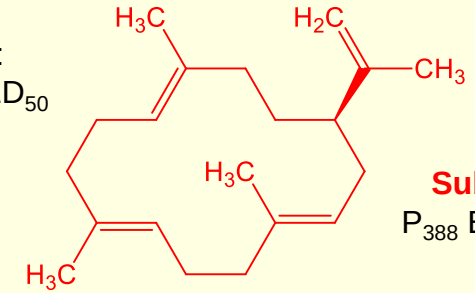
Haliclorensin: Cytotoxic P_{388} IC_{50} = 100μg/mL

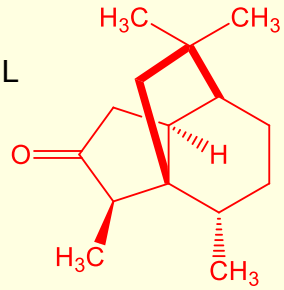


Stoloniferone E: Cytotoxic P_{388} IC_{50} = 0.043μg/mL

Bengazole C6: Cytotoxic MCF7 GC_{50} = 0.06μM

Cembrene A: Cytotoxic L_{1210} ED_{50} = 0.22μg/mL





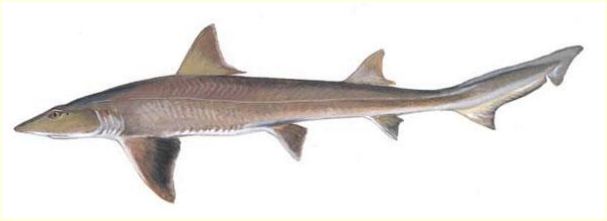
Suberosanone: Cytotoxic P_{388} ED_{50} = 0.000005μg/mL**??**
Trust but verify!!

>30,000 marine natural products have been identified of which >10,000 display interesting bioactivity (~2,000 in vivo bioactive). In 2018, 24 anticancer natural product drug candidates of marine origin were in cancer clinical trials

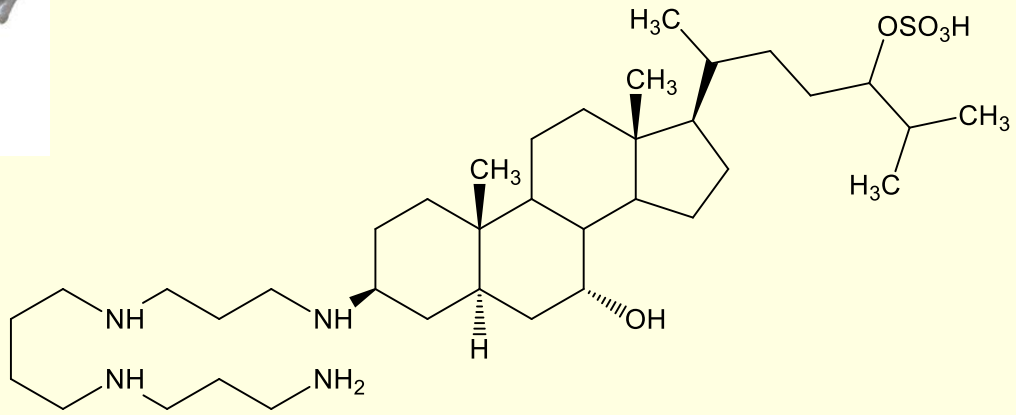
Natural Product Protein Tyrosine Phosphatase Inhibitor - Active In Vivo in Metabolic Syndrome/Diabetes Models

Chonky diabetic Cats

Great companion animal vet medicine opportunity?



Dogfish antibacterial liver extract
a steroid/polyamine hybrid



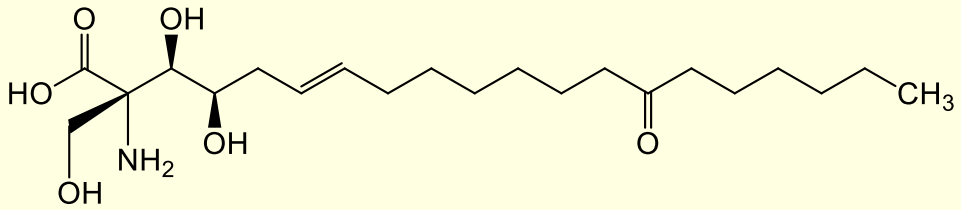
Trodusquemine – **cell permeable selective PTP1B (protein tyrosine phosphatase 1B) reversible, allosteric, inhibitor IC50 = 1.3μM** vs 0% inhibition at 200μM for Tc-PTP. Enhanced IR and STAT3 phosphorylation in cells and tissues. **Decreased appetite, caused weight loss without metabolic rebound, normalized fasting glucose, cholesterol and triglyceride blood levels in obese animal models**. Demonstrated tolerability, good PK profile and safety in a P1 trial**. Abandoned for lack of funding**

Want a Drug with Novel MOA?

Screen Natural Products in Phenotypic Assays!

Stumbling Upon an Unforeseen Molecular Target and Mechanism of Action

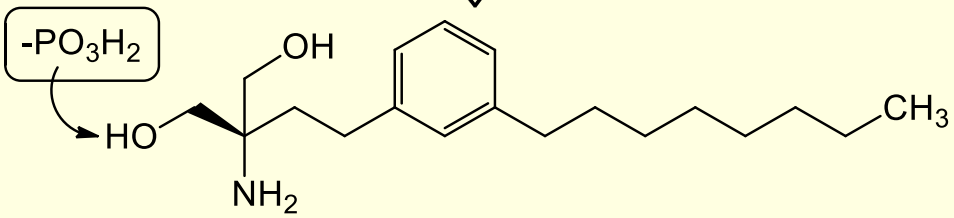
Penultimate Phenotypic Assay



Antifungal ISP-1, myriosin, thermozymocidin (1972)

Broth isolate ISP-1 demonstrated significant activity (10X more potent than cyclosporine) in the standard in **vivo mouse model – the ultimate nonhuman phenotype assay -** of immunosuppression (reported in **1994**)

38 years



Immune suppressant Gilenya

Allogeneic MLR model EC_{50} = 6nM; Protein binding = 99.7%; **XLogP = 6.6**; biological half-life 6-9days; **Oral bioavailability – 93%;** C_{max} =14hr

Prodrug fingolimod; approved by FDA in **2010** (18y after original synthesis); est. 2017 sales **>$2 billion**. Mechanism of action specifically **targets chemokine receptor 7 signaling** leading to selective depletion of mature T-cells by inhibiting cell mobility and causing apoptosis (**Binding to the $S1P_1$ receptor drives CCR-7 receptor internalization – Trafficking MOA**); retention of activated T-cells in the lymph nodes where they accumulate and strongly impact pathophysiology of MS

This is in contrast to supposedly deeply validated Chemokine targets (like CCR1, CCR2, CCR3, CCR4, CCR5) for immune modulation where to date (**2015**) about 40 molecules, many highly potent (low nM) exquisitely optimized drug-like properties (but not in animal efficacy models apparently), have progressed to clinical trials but largely failed to deliver drugs to treat inflammatory and/or autoimmune indications (MS, RA, allergic rhinitis), ***Perfectly validated molecular targets and hyper-optimized molecules does not guarantee a drug in the end!***

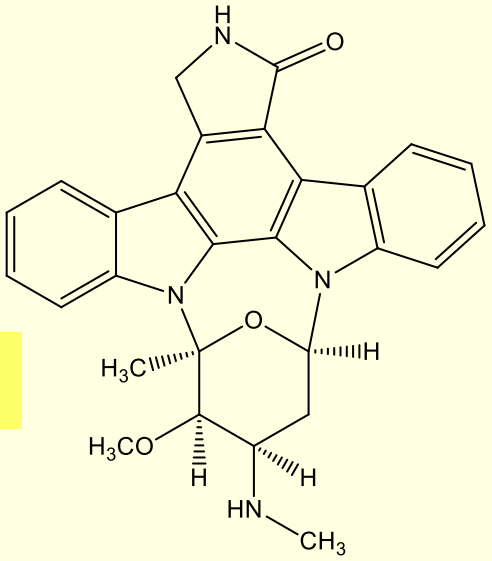
The Natural Products: Am I Selling the Future or Just the Nostalgic Siren Call of Past Glories?

Staurosporine is a prototypical pan-ATP-competitive kinase inhibitor (plus ATPase synapsin-1) in that it binds to many kinases with high affinity (PKC), but with little selectivity (*253 kinases @<3μM*). 100s of analogs have been isolated or synthesized, including a subgroup with a MOA switch to Topoisomerase-1 (no kinase activity - rebeccamycin). Too toxic to be a drug because it stomps all over the kinome tree!

What Pharma sees?

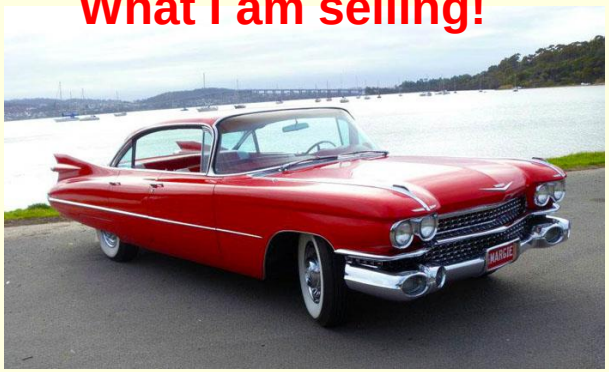
This is the Key Pharma Barrier for NP drugs; not medicinal value to patients, IP or novel bioactivity

Staurosporine
40 years wandering in the biomedical wilderness but natural products can have more lives than two cats



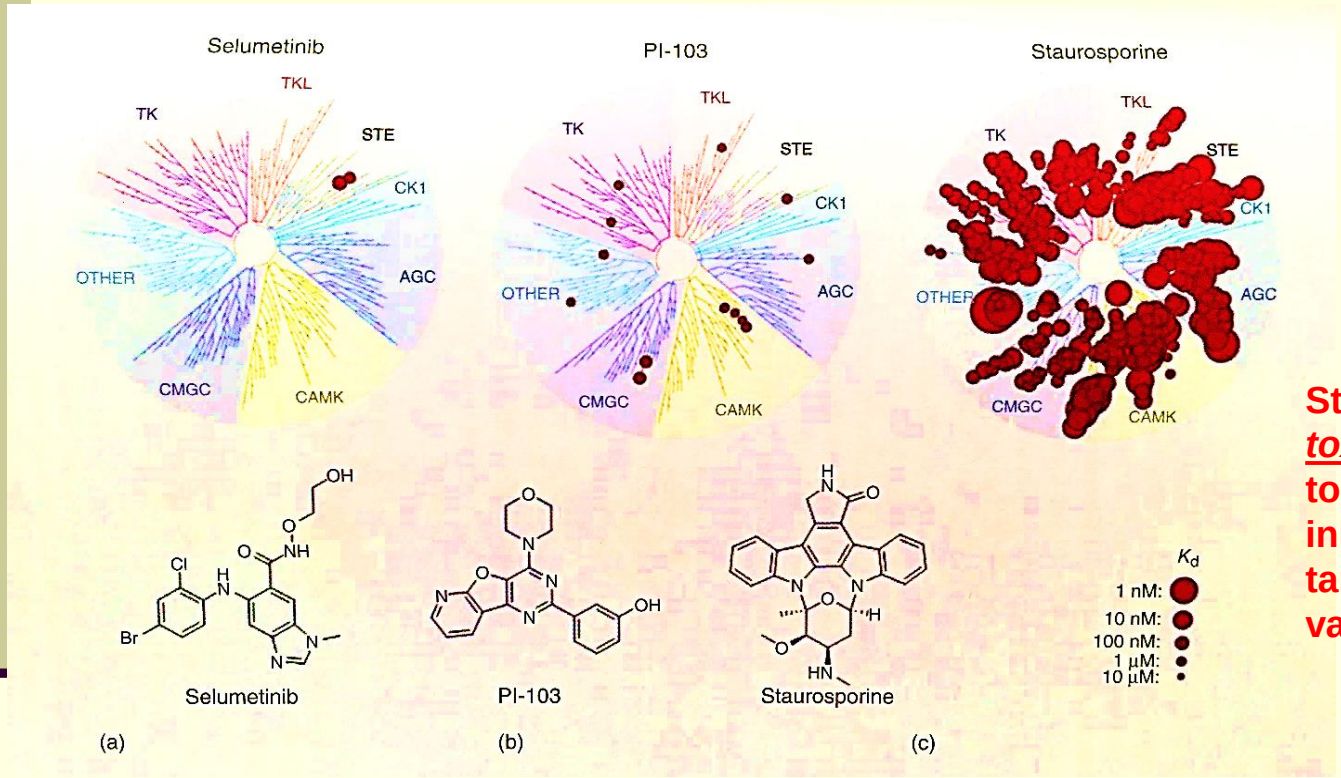
Staurosporine

What I am selling!



Any molecule with biological activity has the potential for commercial success in one of the life-science industries!

Obviously Staurosporine is One Ugly, Dirty Kinase Inhibitor Natural Product That will Never Become a Drug, Right?



Staurosporin will be a *toxic poison* because it is too non-selective, potently inhibiting way too many targets. Is of no medicinal value - kill the program!

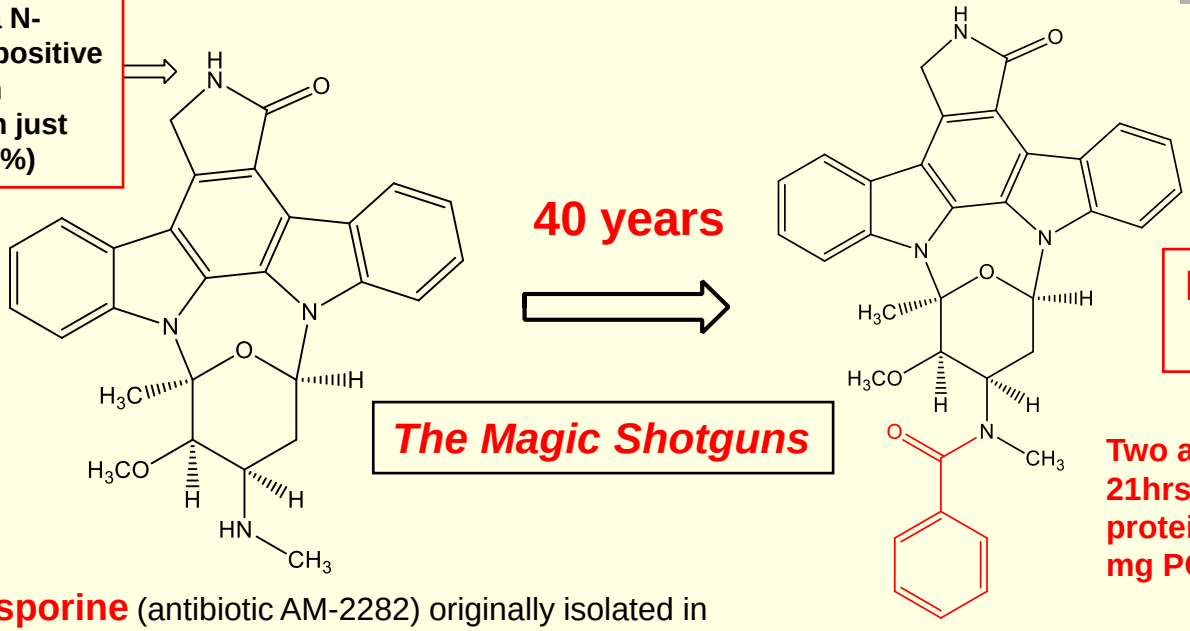
Staurosporin selectivity as seen by binding affinity to various kinases on the kinome tree
Staurosporin has now been re-branded as a druggable multi-targeted protein kinase inhibitor

It is a capital mistake to theorize before one has data – Sir Arthur Conan Doyle

Really? All It Took was One Benzoyl Group and 40 Years?

Revenge of the Toxic, Dirty MOA Natural Product Drugs

Introduction of a N-methyl leads to positive kinase inhibition (<3μM) activity in just 26 out of 223 (11%)



40 years

The Magic Shotguns

FDA Okayed in 2017
Cost ~$90,000/year

Two active metabolites, half-life 21hrs (longer for metabolites), protein binding >99.8%, dose 50 mg PO BID, Patented 2004

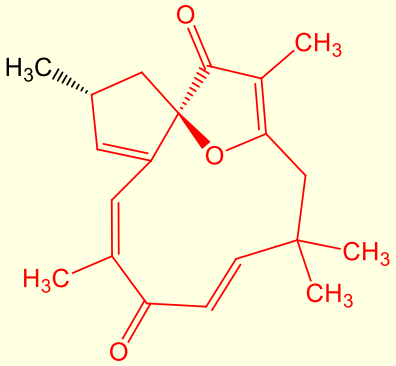
Staurosporine (antibiotic AM-2282) originally isolated in **1977** from the bacterium *Streptomyces staurosporeus.* MOA inhibition of protein kinases. **Staurosporine is a prototypical pan-ATP-competitive kinase inhibitor (plus ATPase synapsin-1) in that it binds to many kinases with high affinity (PKC), but with little selectivity** (**253 kinases @<3μM**). 100s of analogs have been isolated or synthesized including **a subgroup with a MOA switch to Topoisomerase-1(no kinase activity) (rebeccamycin).** With a very dirty MOA, staurosporine demonstrates a wide range of poly-pharmacology including **antimicrobial, antifungal, cytotoxicity, platelet aggregation inhibition and antihypertension activity**. **Too toxic to be a drug!**

Midostaurin (**Rydapt**/oral) is a **multi-targeted protein kinase inhibitor** (FLT3/PKCα/KIT/PDGFRα/β/+more). It is a semi-synthetic derivative of staurosporine. It was found to significantly **prolong survival** of FLT3-mutated AML patients when combined with conventional induction and consolidation therapies in a randomized Phase III clinical trial. In **2017**, midostaurin was approved by the FDA for the treatment of adult patients **with newly diagnosed AML who are positive for oncogenic FLT3,** in combination with chemotherapy. Re-sensitizes MDR phenotype cancer cells to cytotoxic drugs. **Analogs enzastaurin, ruboxistaurin and sotrastaurin are in clinical trials**

My 60 Year Love Affair with Biologically Active Natural Products – My Career

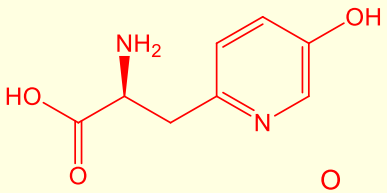
PhD Advisor, Mentor, Inventor of **Irofulven** and True Gentleman: **Professor Trevor McMorris**

Steroid isolated from soft coral from Canton Island potent anticancer cytotoxin

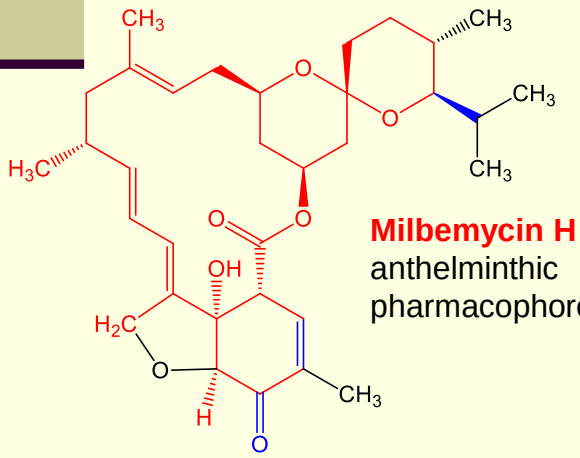


Cytotoxic anticancer diterpene **jatrophone**

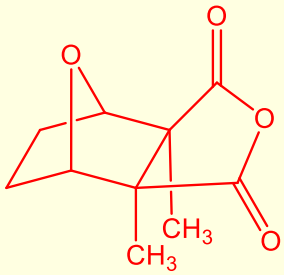
Batrachotoxin frog arrow dart toxin Na-channel opener pharmacophore approach



Azatyrosine reverts *ras*- or c-erbB-2 transformed phenotype cells to normal



Milbemycin H anthelminthic pharmacophore



Cantharidin - inhibitor of protein phosphatases 1 and 2A from blister beetles.

GSH – colchicine hybrid – GSTPp-1 targeted tubulin inhibitor