



- Small-molecules in drug discovery  
- real life examples

- Navigating in ADME space towards **new medicines**
- How do you find a **lead**?
- ... and how do you make that into a **drug**?
- ... and how about **intellectual property rights**?

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Frederiksberg, January 31, 2017  
Dias 1



## How much money are drugs worth?

THE 30 TOP-SELLING DRUGS ON THE MARKET				
No	Biotech	Small molecule drug	Name	Company
1	11		Humira	AbbVie
2	8,75		Enbrel	Amgen
3		8,3	Advair	GSK
4	8,3		Remicade	Johnson/Janssen
5	8		Rituxan	Roche/Genentech
6	7,5		Lantus	Sanofi
7	6,5		Avestin	Roche
8	6,5		Herceptin	Roche/Genentech
9		6	Crestor	AstraZeneca
10		6	Junuvia	Merck & Co
11		5,5	Abilify	Otsuka
12		5	Cymbalta	Eli Lilly
13		4,5	Gleevec	Norvatis
14		4,5	Lyrice	Pfizer
SUM	56,55	39,8		



## Average life expectancy over time

<i>Humans by Era</i>	<i>Average Lifespan at Birth (years)</i>	<i>Comment</i>
Upper Paleolithic	33	At age 15: 39 (to age 54)
Neolithic	20	
Bronze Age	18	
Bronze age, Sweden	40-60	
Classical Greece	20-30	
Classical Rome	20-30	
Pre-Columbian North America	25-35	
Medieval Islamic Caliphate	35+	The average lifespans of the ruling class were 59–84.3 years in the Middle East and 69–75 in Islamic Spain
Medieval Britain	20-30	
Early 20th Century	30-40	
Current world average	70 (2008 est.)	

What is the reason for the dramatic change in the early 20th century?



## Drug Discovery, design and development: the past

Before the 20th century, medicines mainly consisted of herbs, extracts and potions. There were **no knowledge** of the **active principle** or the **mechanism-of-action**.

Typical examples from Nature could be:

- Salicylates (and later Aspirin®) from the bark of willow
- Morphine from opium
- Cocaine from coca leaves
- Quinine from the bark of the cinchona tree (*Cinchona officinalis* L.)
- Penicillin from the mold *Penicillium notatum*
  
- ...and much later, *e.g.*
- Paclitaxel (Taxol®) from the Pacific Jew Tree

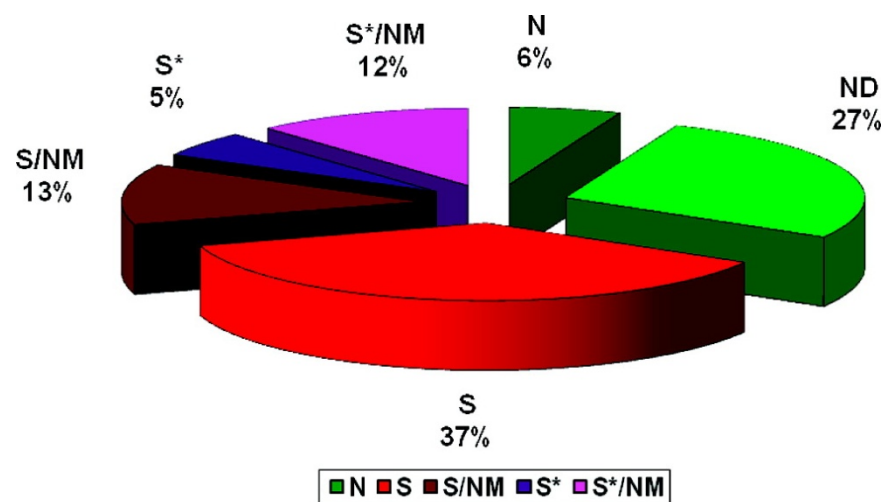


## The continuing role of Nature in Drug Discovery

The latest analysis covers 1024 new chemical entities (NCE's) from January 1981 to the middle of October 2008, an increase of 50 small molecules in the two years.

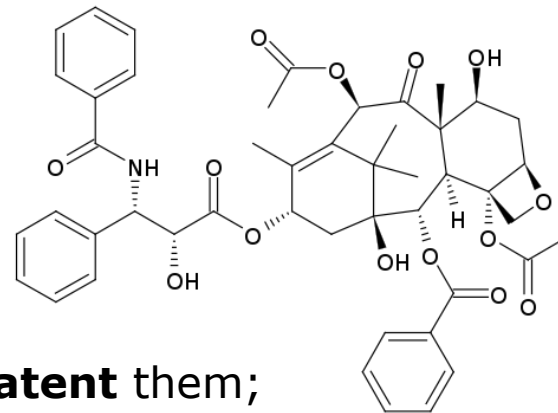
From the current data, **67% of the compounds are formally synthetic**, but the analysis indicates that 18% of these correspond to the S\* and S\*/NM classes (NP pharmacophore) and 13% fall into the S/NM class (model a natural product inhibitor of the molecular target of interest, or mimic, as they are competitive inhibitors, the endogenous substrate of the active site).

Thus, as with the 2007 analysis, the proportion of truly synthetic (*i.e.*, devoid of natural product inspiration and coded as S) is still at 37%



## Natural product advantages

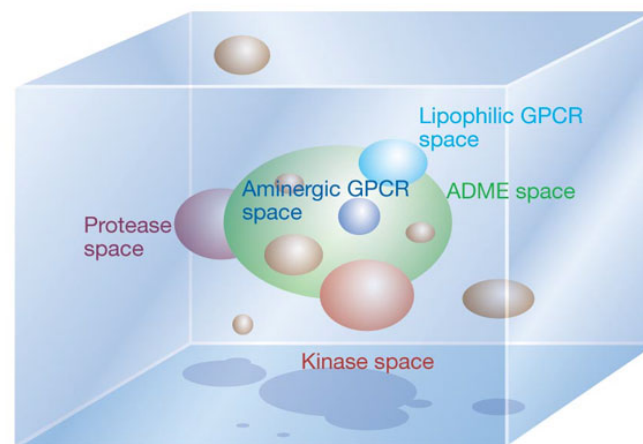
- Evolution → there is a reason for the host making these compounds. They are truly not made just for fun.
- Superb diversity! Would you come up with the structure of paclitaxel just by chance??



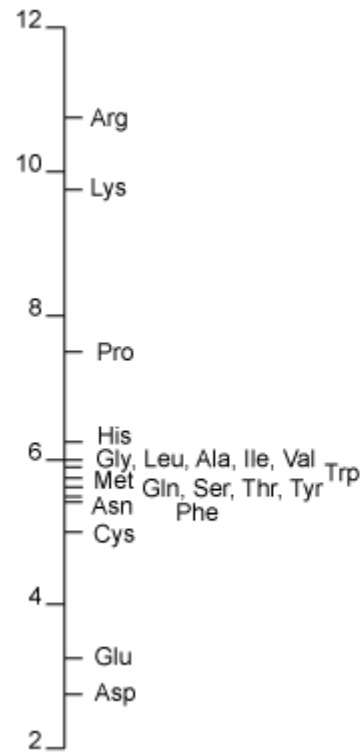
- Unique structures → you can **patent** them;
- Less flexible → when they work, they work better!
- Experience in society (shaman, witch doctor, traditional folklore medicine, etc.)

## Chemical Diversity

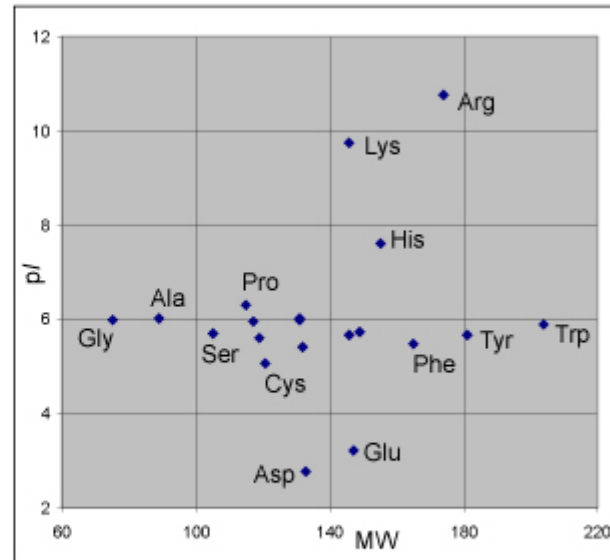
- A set of descriptors used to qualify and/or quantify the extent of variety within a set of compounds.
- The opposite of similarity (which is somewhat easier to comprehend)
- Chemical space, relevant chemical space or ADME-space
- “ADME”? or “ADMET”?



## Chemical Diversity based on properties



1D



2D

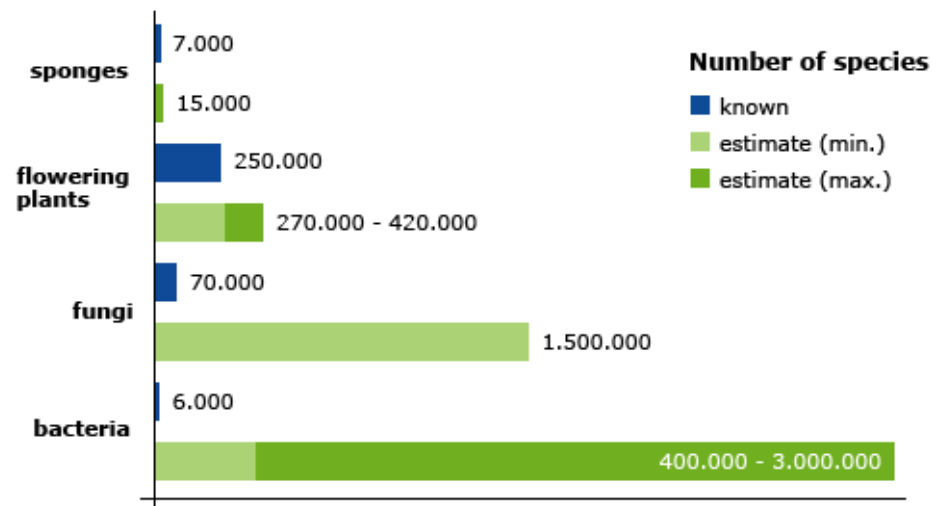




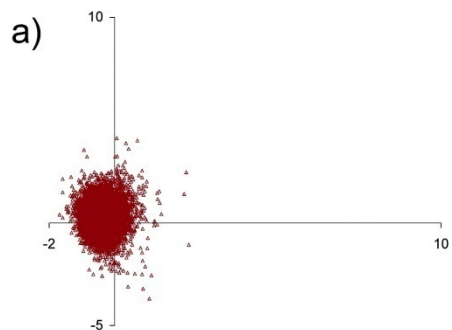
## Why Natural Products?

Natural Products (NP) represent the diversity of nature that is unsurpassed by synthetic material.

NP chemical structures have been optimized through the processes of evolution, frequently resulting in entities with unique and highly specific bioactive properties. NPs thus complement synthetic sources. In addition, while about 220,000 NP compounds are presently known to science, the vast majority of biological sources have not even been thoroughly investigated yet. Nature is therefore a vast potential reservoir in the search for bioactive **lead compounds**.

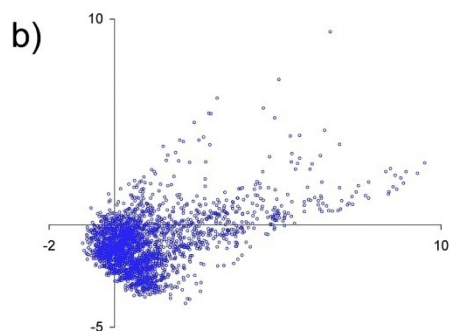


## Properties of combinatorials vs natural products and drugs

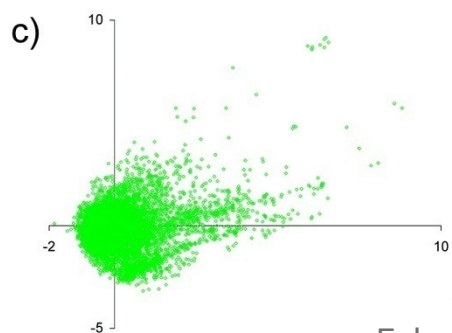


The plot of the first two principal components, obtained from a database containing:

a) a random selection of combinatorial compounds ( $n = 13,506$ )



b) natural products ( $n = 3,287$ )



c) drugs ( $n = 10,968$ )

Feher and Smith (2003) *J. Chem. Inf. Comput. Sci.* **43**, 218-227



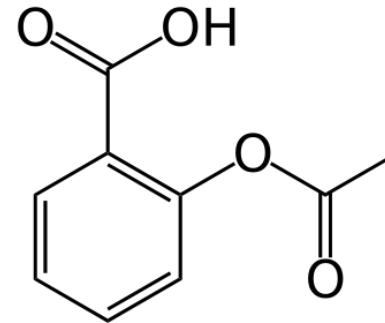


## Discovering leads and making drugs

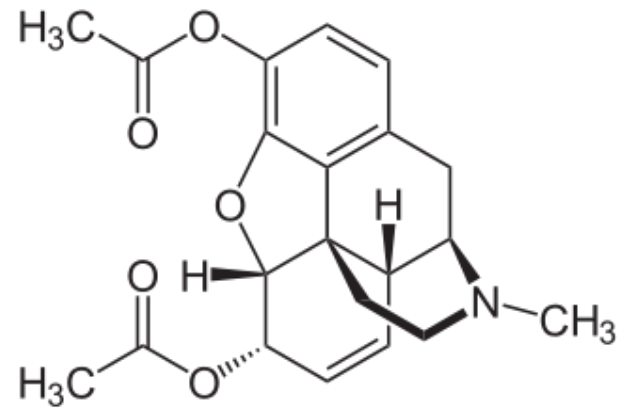
- Aspirin
- Penicillin

## Aspirin®

- Known and used since 3000 BC as a preparation and extract from the bark of willow (salicin and salicylates);
- Synthesized in 1853 by Charles F. Gerhardt (AcCl + sodium salicylate)
- Introduced to the market in 1899 as a medicinal drug by the German dye and pharma giant Bayer.
- Originally introduced as a protected trademark (Aspirin®)
- The name originates from Acetylation and Spirsäure (from *Spirea*)
- Very useful during the Spanish Flu pandemic (1918) – due to its antipyretic properties.



## Acetylation of natural products – a magic bullet?



Am. J. Ph.]

7

[December, 1901

### BAYER Pharmaceutical Products **HEROIN—HYDROCHLORIDE**

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, \$4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

**The Cheapest Specific for the Relief of Coughs**  
(In bronchitis, phthisis, whooping cough, etc., etc.)

WRITE FOR LITERATURE TO

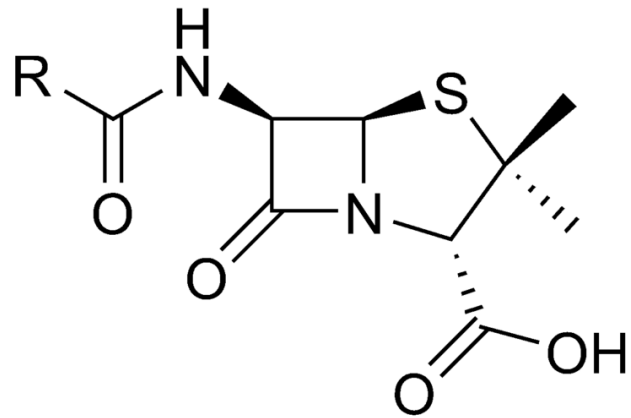
**FARBENFABRIKEN OF ELBERFELD COMPANY**  
SELLING AGENTS

P. O. Box 2160

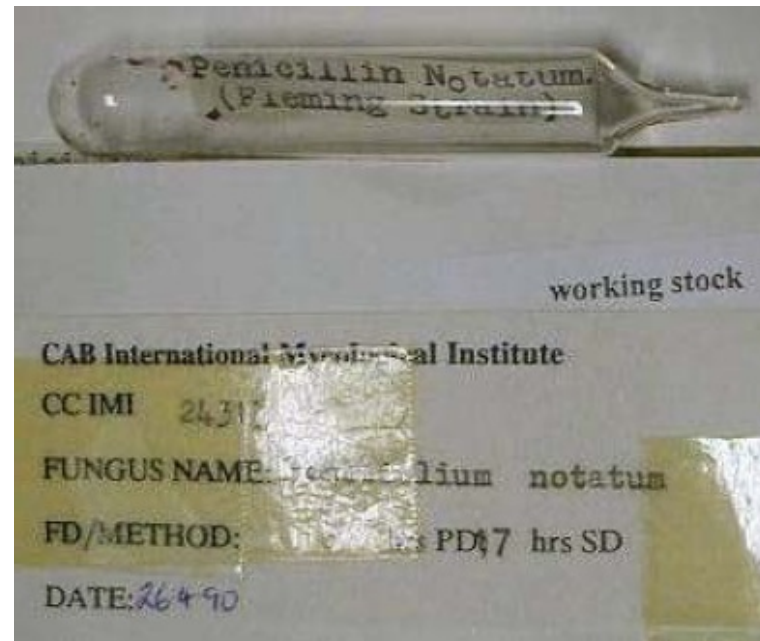
40 Stone Street, NEW YORK



## Penicillin



Penicillin was discovered by the Scottish scientist Alexander Fleming (NL 1945), on 28/9 1928, when he found a Petri dish with staphylococcus fault fully contaminated by mold – and showing a clearing zone around the mold. Penicillin is mostly effective against gram-positive bacteria.



From CABI Bioscience UK Center, where they still keep a life sample of Fleming's strain.

## How are drugs discovered and developed?

- **Select a disease!**
- Identify a drug target ("a drugable target")
- Develop a bioassay
- Find hits and lead compounds
- Optimize hit-to-lead – and develop lead
- Identify the pharmacophore
- Improve target interactions (pharmacodynamics)
- Improve compound stability and properties (pharmacokinetics, ADME)
- **Patent the drug**
- Pre-clinical trials
- Manufacturing and production
- Clinical trials (phases I, II and III)
- Registration, approval and marketing → **making money**



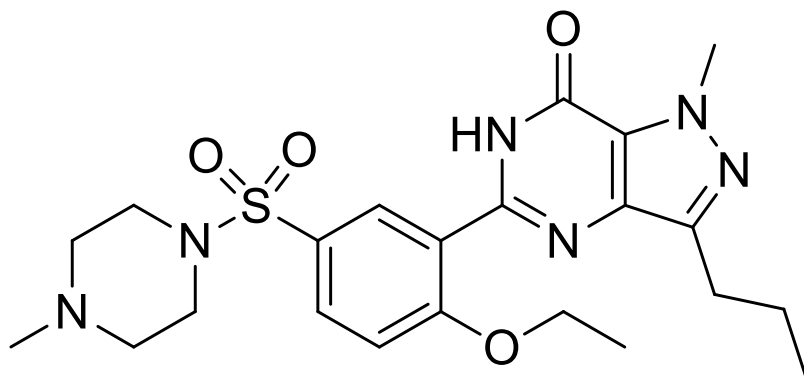
## How are leads discovered?

- Natural products – shaman, witch doctors, traditional medicine (India, China, etc.)
- Natural products – *brut force* screening
  - Plants
  - Microorganisms (bacteria, fungi)
  - Marine sources (sea, river, lake, geysers, etc.)
  - Animals (poison, toxins, etc.)
- Synthetic compounds – *brut force* screening
  - Synthesis (*de novo*)
  - Basement collection
  - Acquisition
- Combinatorial chemistry (compound libraries)
- Side effects (useful ones, though!)
- Me-too products
  - **Reading other companies patents**

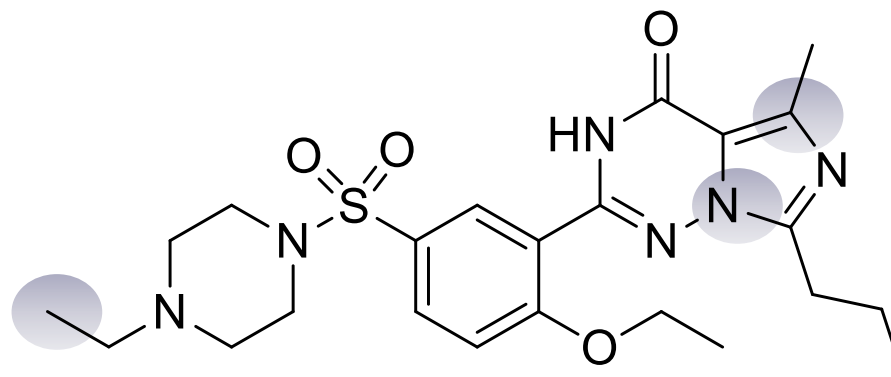




*Me-to* example: sildenafil



Sildenafil  
(Viagra™, Pfizer)



Vardenafil  
(Levitra™, Bayer AG)

## New trends – multimodal drugs

- Multi-target drugs are drugs that hit more than one pathway relevant for the treatment of a given disease
- Typically, this has been obtained by administration of more than one drug (example: Augmentin containing both amoxicillin and clavulanic acid)
- Alternatively, it has been tried to combine two drugs with a chemical linker (dual action drugs)
- Finally, some drugs modulate a number of different biological targets simultaneously.
- Previously, the drugs had a different name .....
- ...**promiscuous ligands** or **dirty drugs!**
- ...but now this field has been renamed: **Polypharmacology!**





## Discovering leads and making drugs

- Varenicline (Champix®)

## Discovering an anti-smoking agent – the need

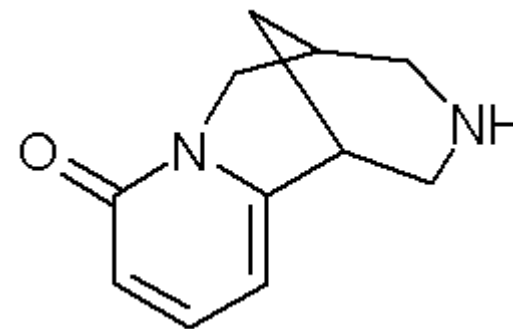
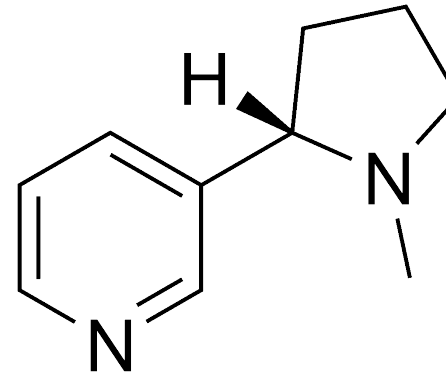
**Nicotine** targets the nicotinic receptors located in the brain thought to be central to the reward and habituation. **Dopamine release!**

A specific abundant subtype of the nACh-receptor, termed  $\alpha_4\beta_2$ , is believed to increase the reinforcing properties of nicotine

**Cytisine** is a toxic plant natural product (alkaloid) with nicotine-like biological activity.



Tobacco

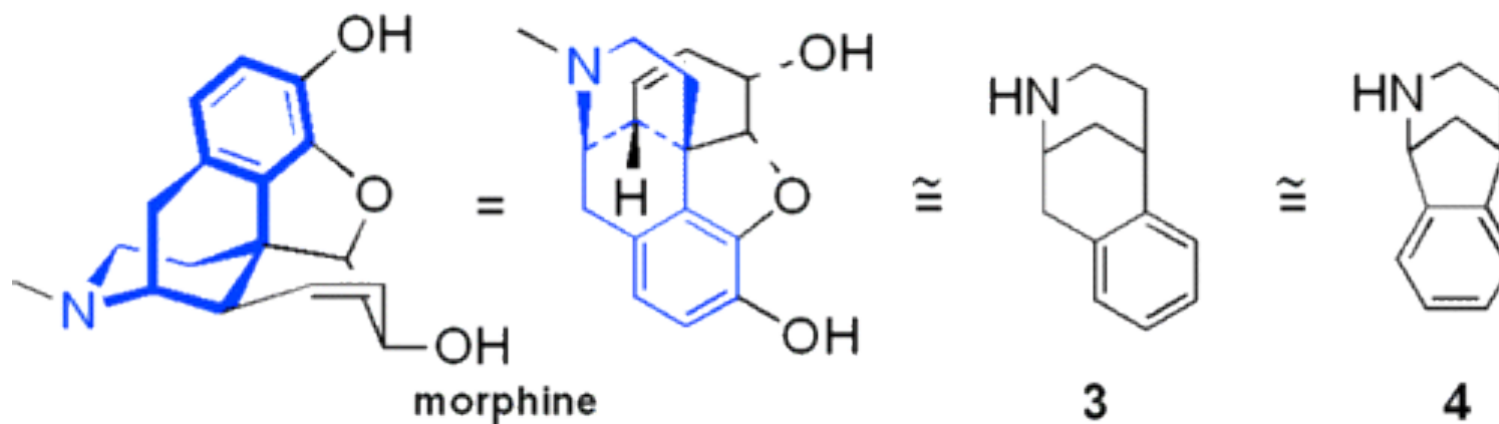
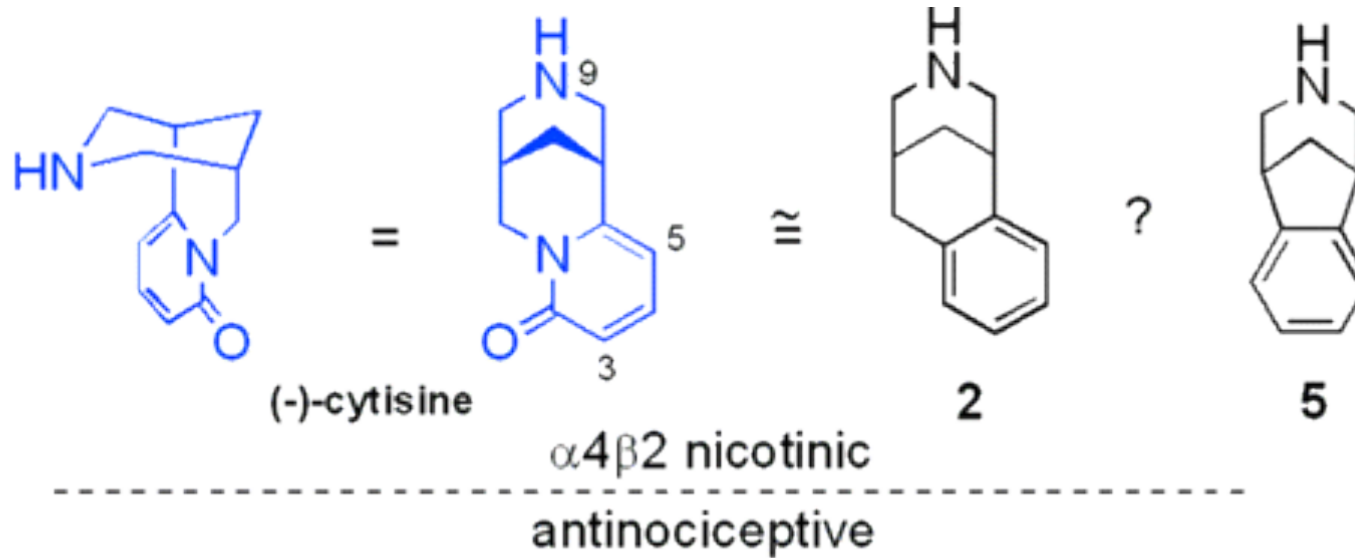


Mescalbean



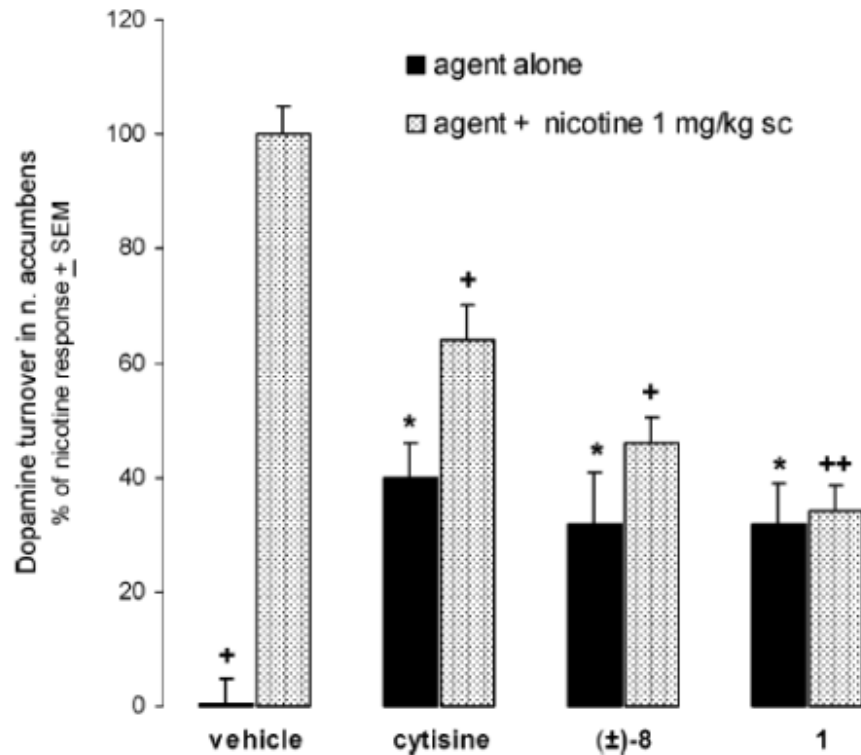
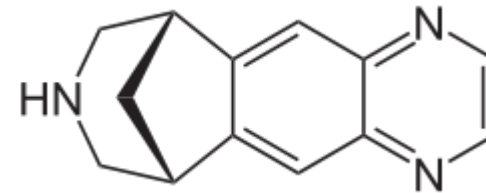
Māmane (*Sophora chrysophylla*)

## Pharmacophore analysis and design

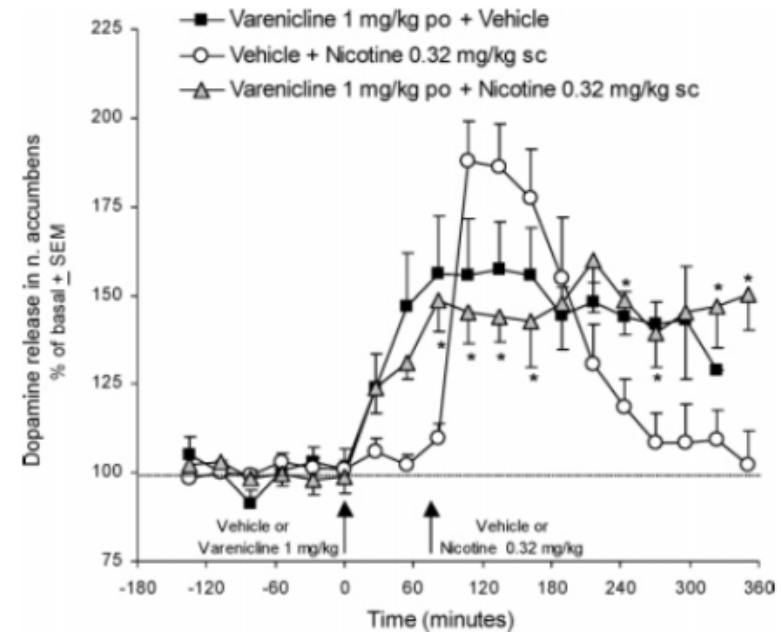


## Discovering an anti-smoking agent – discovery and development

Chemical synthesis → a collection of chemical entities including **varenicline**



Effects of (-)-nicotine, (-)-cytisine, (±)-8, and **varenicline (1)** on dopamine turnover in rat nucleus accumbens 1 h postdose



Time courses for the effects of nicotine (open circles) and **varenicline (1)**, filled squares) alone and in combination (triangles) on extracellular dopamine levels in rat nucleus accumbens.



## Varenicline → Champix

Cigarette smoking is the most important source of preventable and premature morbidity worldwide. Currently, the number of smokers across the globe is estimated at 1.3 billion. Political moves are leading to national bans of smoking in public places, with the long-term aim to reduce the cost to the health sector. But what will be the short-term spending on smoking cessation therapies?

In 2007 Visiongain believes the anti-smoking market to be worth **\$1.7 billion**. This is a growth of 37% from the year before. This latest report from Visiongain, Global Smoking Cessation Market Analysis & Forecasts - preparing for the first blockbuster, explains just how this market will experience growth over the medium term future. Also do you know what the drivers and restraints of the market are? This report not only reveals these, but also details what strategies can be used to maximize profits from the drivers and restraints.

