MOLECULAR PRINCIPLES OF DRUG DESIGN

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MUNI PHARM

THE THEORY OF PRIVILEGED STRUCTURES & CHEMOGENOMICS

PRIVILEGED STRUCTURES

Privileged structure is
a single molecular framework
able to provide ligands for diverse receptors, from which can be obtained
new receptor agonists and antagonists
by rational modification.

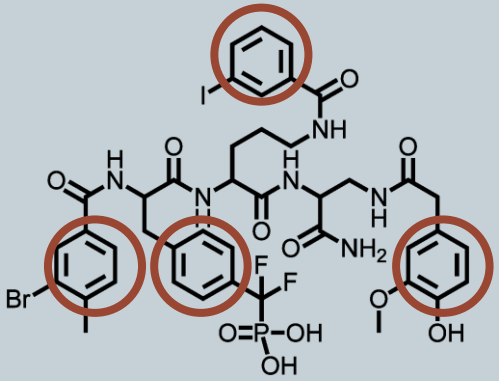
Evans & co., 1988

Characteristics of privileged structure

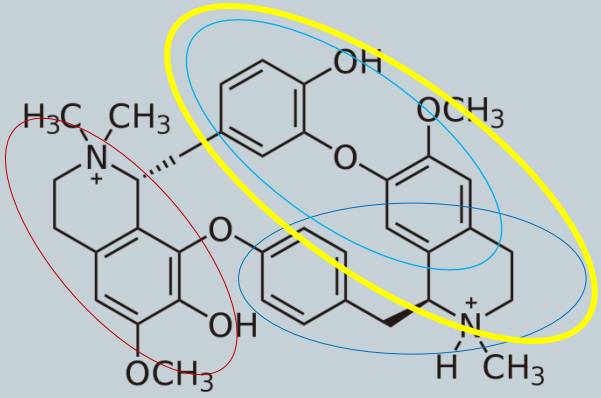
- Small
- Non-planar
- Robust conformation
- Provides interesting 3D exit vectors for substitution
- Drug-like properties
- Constitutes a significant portion of the total mass of the molecule
- Ideally readily accessible synthetically

Characteristics of privileged structure

- Cyclic structures are ideal scaffolds for drug development
  - Molecular rigidity (need lower energy for new bond forming)
  - Better bioavailability
  - Bicyclic and tricyclic molecules have ideal size for library synthesis



- Cyclic structure - usually has 2-3 rings
  - Condensated or linked by one or two bonds
  - Usually substituted by phenyle
  - Usually contains a heteroatom



Characteristics of privileged structure

- Molecules with therapeutical effect = drug-like properties
- Lipinski's rule of five (Pfizer's rule of five, RO5)
  - Molar mass < 500 g/mol
  - logP < 5 (lipophility)
  - Donors of H-bonds <5
  - Acceptors of H-bonds <10 (2x5)
- Physiochemical characteristics for promiscuous binding
- Smaller molecule has higher capacity of binding to multiple receptors
- Simple ligand surface

Promiscuous ligands

Promiscuous ligands

- potently
- specifically
- reversibly
- but not selectively

bind to the members of different macromolecular target families.

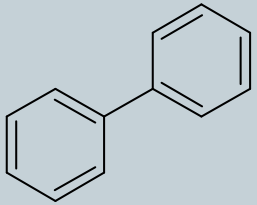
PRIVILEGED STRUCTURE

x „drug-like“ structure

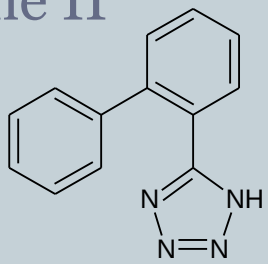
x non-specific „protein-binder“

Bonding and specifity

- (sub)structure provides bonding on protein
- linked SUBSTITUENTS are responsible for receptor specifity



  - Structure of biphenyle was described as privileged (sub)structure – it can be found in 4,3 % of all known drugs with different biologic activity
  - 2-tetrazolobiphenyle: part of cca 1/5 drugs with biphenyle; those drugs mainly block receptor for angiotenzine II



Why are so interesting?

- Modeling of potential “small molecules”
  - Molecules with low molar mass (<500 Da)
  - Number of possible small molecules is 10^{200}
  - Drug-like properties may have 10^{60}
- New drug targets
  - Target structures newly discovered by genetics, proteomics,…
  - Better information about known diseases
- Bring a new drugs to the pharmaceutical market
  - Drugs for new diseases
  - The development of a new drug takes a long time and is expensive
- Structural libraries

Example of finding a privileged structure

- Analyses of ChEMBL22 database
- 1.397.535 compounds
- 181.888 scaffolds

- The most frequent scaffold was a single phenyle ring
- Group 1:
  - 2 rings closely linked (methyl, ether, amine, amide)
  - Similar observation for natural products
  - In 12 % drugs with Mr<2000 approved by FDA (1939-2006)
- Group 2:
  - A lot of them target-specific
  - Can be told privileged structures?
- ↑ number of sp^3 atoms and H-bond acceptors = ↓ promiscuity

Cit: Schneider, P., Schneider, G.: *Privileged Structures Revisited*. Angew. Chem. Int. Ed. 2017, 56, 7971-7974

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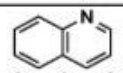
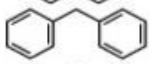
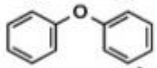
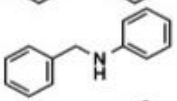
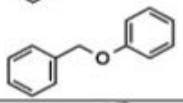
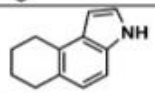
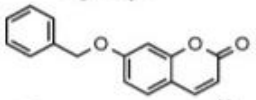
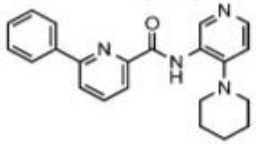
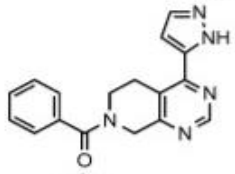
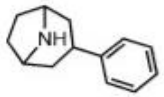
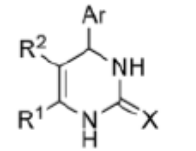
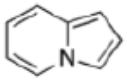
1a		285	yes
2a		545	
3a		1184	yes
4a		245	
5a		828	yes
1b		280	yes
2b		282	yes
3b		103	
4b		190	
5b		870	

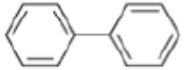
Examples of privileged structures



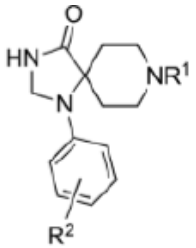
Dihydropyrimidone
[X = S or O]



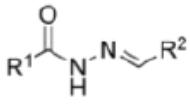
Indolizine



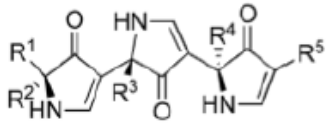
Biphenyl



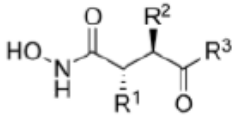
Triazaspirodecanone



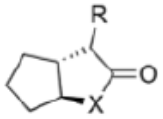
N-Acylhydrazone



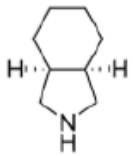
Pyrrolinone



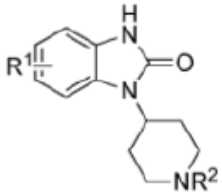
Hydroxyamate



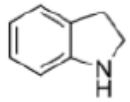
trans-Lactam/Lactone
[X = N or O]



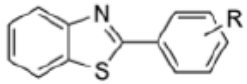
Hexahydroisoindole



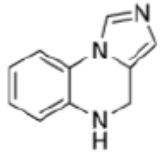
Benzimidazolone



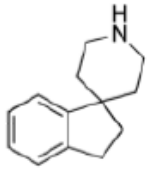
Indoline



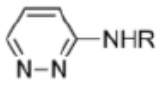
2-Arylbenzothiazole



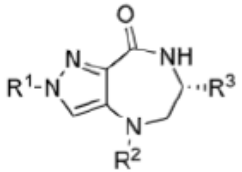
Imidazolequinoxaline



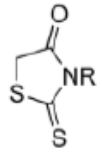
Spiroindanylpiperidine



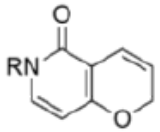
Aminopyridazine



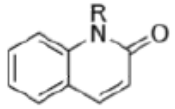
1,4-Pyrazolodiazepin-8-one



Rhodanine



Pyranopyridone

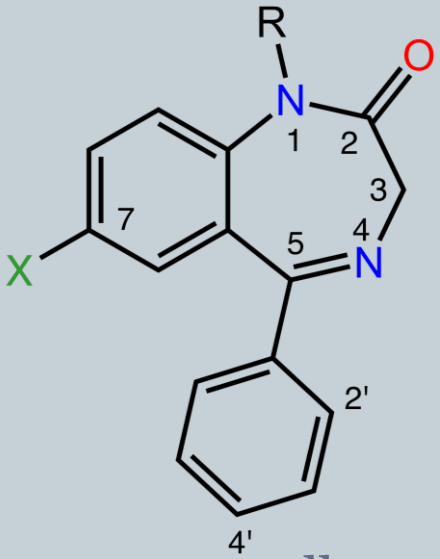


Pyranoquinolone

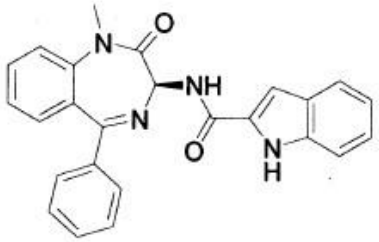
„The first one“

1,4-benzodiazepin-2-on

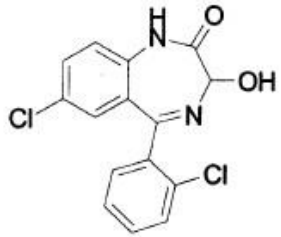
- Small library of 192 molecules => cholecystokinin A receptor => several active compounds (Ellman, early 90s)
- Larger library of 1680 compounds (Welsch, 2010)
- Targets
  - Cholecystokinin (*devazepine*)
  - Gastrin
  - Central benzodiazepine receptors (*lorazepam*)
  - Neurokinin-1 antagonistS
  - K-secretase inhibitors
  - Farnesyl:protein transferase inhibitors
  - Delayed rectifier K+ current modulator



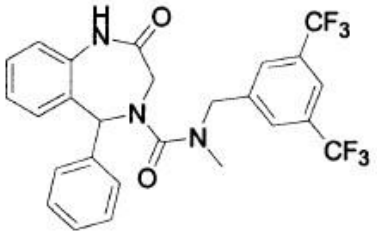
- It is thought to be the privileged due to its ability to structurally mimic beta peptide turns (Ripka, 1993)



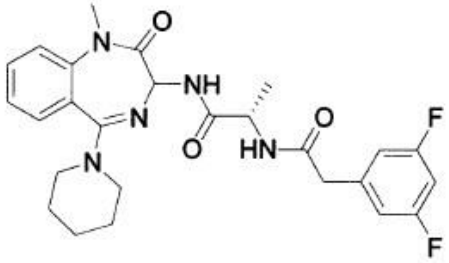
1
Devazepide
CCK-A Antagonist



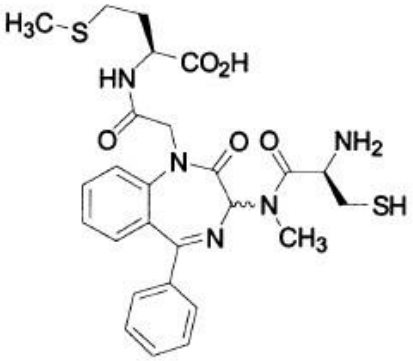
2
Lorazepam
Benzodiazepine Agonist



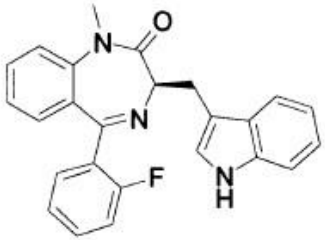
3
Neurokinin-1 Antagonist



4
κ-Secretase Inhibitor

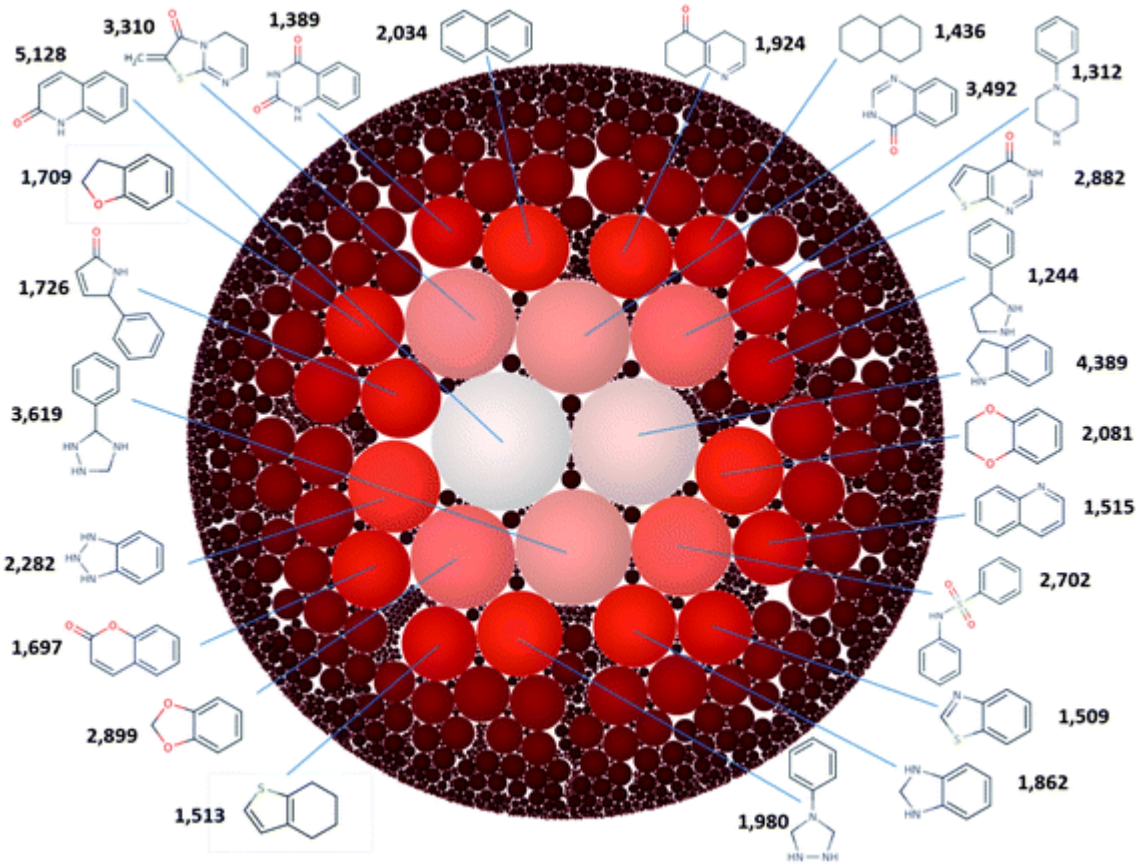


5
Farnesyl:Protein Transferase
Inhibitor



6
Delayed Rectifier K^+
Current Modulator

LIBRARIES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1,726
1,244
4,389
3,619
2,081
1,515
2,282
2,702
1,697
1,509
2,899
1,862
1,513
1,980

Structural library

Structural / chemical /compound library
is a collection of stored chemicals.

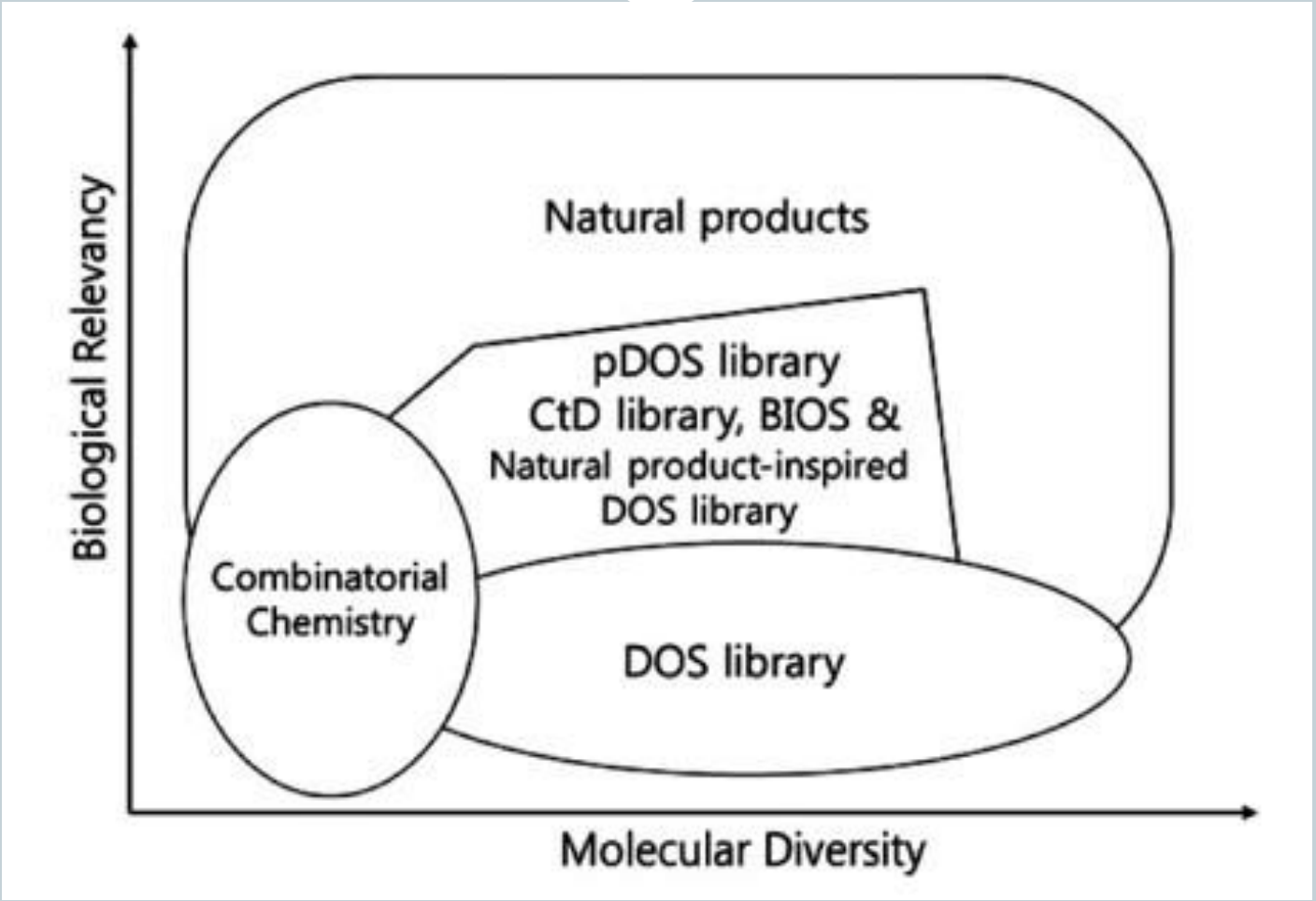
- Can consist in simple terms or a series of stored chemicals.
- Each chemical has associated information stored in some kind of **database** with information such as
  - the chemical structure
  - purity
  - quantity
  - physiochemical characteristics of the compound.

Structural library

Natural sources: huge diversity of compounds, biologicly active, but mostly limited spectre of effects (over-specialized)

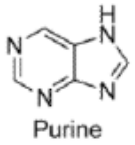
Synthetic sources: derived from privileged scaffolds, synthetic compounds with proven biologic activity, structures proven by molecular modelling, etc.

Structural libraries



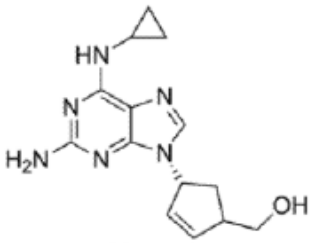
1. Library based upon one core scaffold

Screening of one molecule and its derivatives against a variety of different targets

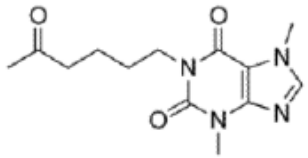


Purine

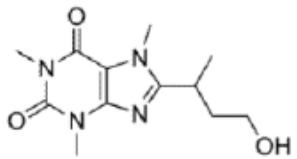
Drugs



Abacavir
Therap Cat: Antiviral (HIV)

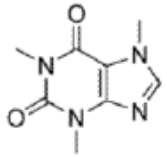


Pentoxifylline
Therap Cat: Hemorheologic agent

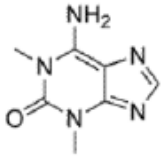


Cafaminol
Therap Cat: Decongestant (nasal)

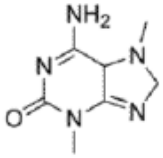
Natural Products



Caffeine
Source: Coffee beans, tea leaves
Biological Activity: Stimulant



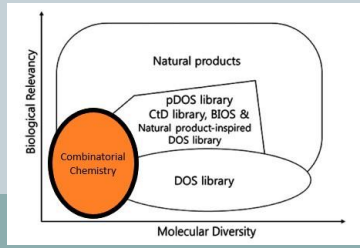
1,3 Dimethylisoguanine
Source: Amphimedon viridis
Biological Activity: Cytoxic to human ovarian cancer cells



3,7 Dimethylisoguanine
Source: Agelas longissima
Biological Activity: Antibacterial

2. Combinatorial chemistry

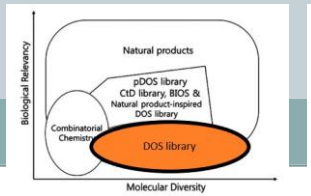
- Comprises chemical synthetic methods that make it possible to prepare a large number (tens to thousands or even millions) of compounds in a single process.
- **High-Throughput Screening** (HTS)
  - Method for biological testing large chemical libraries
  - Using robotics, data processing/control software, liquid handling devices, and sensitive detectors, high-throughput screening allows a researcher to quickly conduct millions of chemical, genetic, or pharmacological test
  - The microtiter plate: a small container, usually disposable and made of plastic, that features a grid of small, open divots called *wells* (multiples of 96)

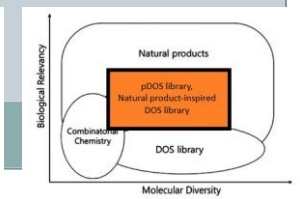


3. DOS a pDOS libraries

Resulting libraries contain complex and diverse structures with a high fraction of sp3-hybridized carbon atoms and more stereogenic centers.

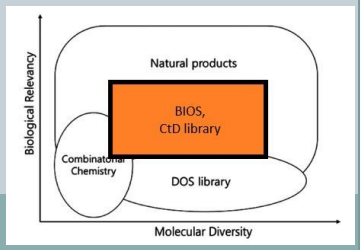
- **Diversity Oriented Synthesis**
  - Apply a variety of reaction conditions to starting materials with multiple different functional groups
  - Multiple rounds of such reactions result in rapid access to structurally diverse products suitable for screening
- **Privileged-substructure-based Diversity Oriented Synthesis**
- **Natural product-inspired DOS library**





4. BIOS and CtD

- **Biology Oriented Synthesis**
- **Complexity to Diversity**
  - Use of core structures derived from bioactive natural products as synthetic scaffolds
  - Structural motif and core skeletons from bioactive natural products can serve as chemical “navigators” for the synthesis of novel core skeletons
  - Construction of natural product-like small-molecule collections starting from commercially available natural products (abietic acid, adrenosterone, quinine)



CHEMOGENOMICS

=

the discovery and description of

all possible drugs

for

all possible drug targets

CHEMOGENOMICS

aims towards
the systematic identification
of small molecules
that interact with the products of genome
and
modulate their biological function

Some definitions

- GENOMICS = an interdisciplinary field of science focusing on the structure, function, evolution, mapping, and editing of genome
- Genome = a genome is an organism's complete set of DNA, including all of its genes
  - Human Genome Project (1990-2003): identification of 20 000-25 000 genes in human DNA
- Genetics = study of individual genes and their role in inheritance

- PROTEOMICS = refers to the large-scale experimental analysis of protein
- Proteome = the entire set of proteins that are produced or modified by an organism or system

More definitions

- Chemical genomics / CHEMOGENOMICS
  - the systematic identification of small molecules that interact via a specific molecular recognition mode with target proteins encoded by the genome
  - the term **chemogenomics** is applied more specifically to target family approaches in drug discovery
- Chemical genetics
  - identify chemical compounds which induce or revert specific biological phenotypes by using cell-based or microorganism-based screening of compound
- Chemical biology
  - the functional and mechanistic investigation of biological systems using chemical compounds and constitutes a more general discipline

Chemogenomic terminology

- 1996
- Company Glaco Wellcome

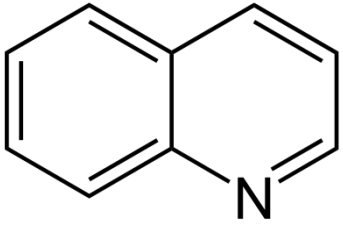
- Systematization of drug discovery within target families based on the analysis of gene families
  - Enzymes
    - Kinases
    - Proteases
  - GPCRs (receptors conected with G-proteins)
  - Nuclear receptors
  - Ion channels
  - Transport proteins

Traditional approach

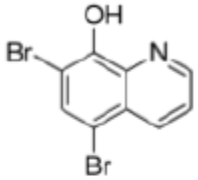
- Based on therapeutic areas
- Genomically unrelated targets are addressed together
- Example: therapy of neurodegenerative diseases
  - Acetylcholine and its derivarives
  - Antagonists of muscarinic and nicotinic receptors (target = **receptor)**
  - Inhibitors of acetylcholinesterase (target = **enzyme**)
  - Inhibitors of β-amyloid agregation (target = **small protein**)

Chemogenomic approach

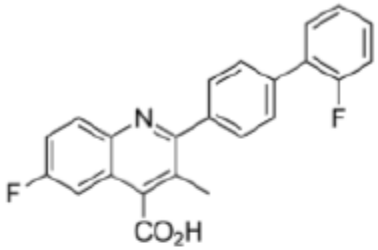
- Analysis does not depend on knowledge of biological function
- Members of the same protein family can share important practical aspects
- Similar ligands should bind to similar targets → knowledge previously obtained → transferable to new related projects



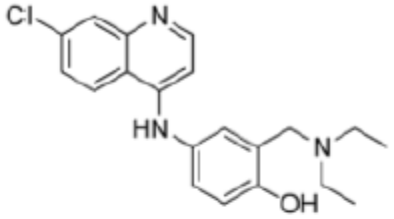
Drugs



Broxyquinoline
Therap Cat: Antiseptic; disinfectant

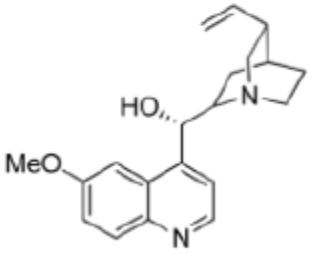


Brequinar
Therap Cat: Immunosuppressant

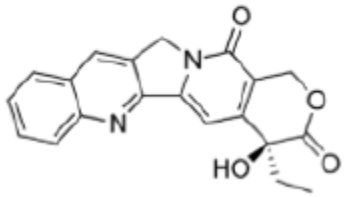


Amodiaquin
Therap Cat: Antimalarial

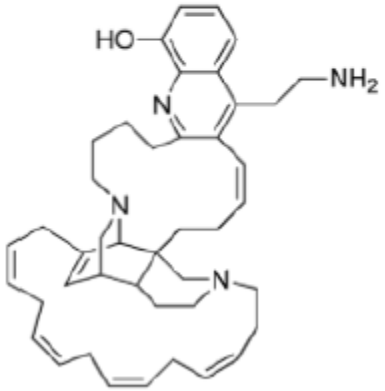
Natural Products



Quinine
Source: Quina Bark
Biological Activity: Anti-malarial



Camptothecin
Source: The Chinese tree Camptotheca acuminata Decne
Biological Activity: Anti-cancer activity

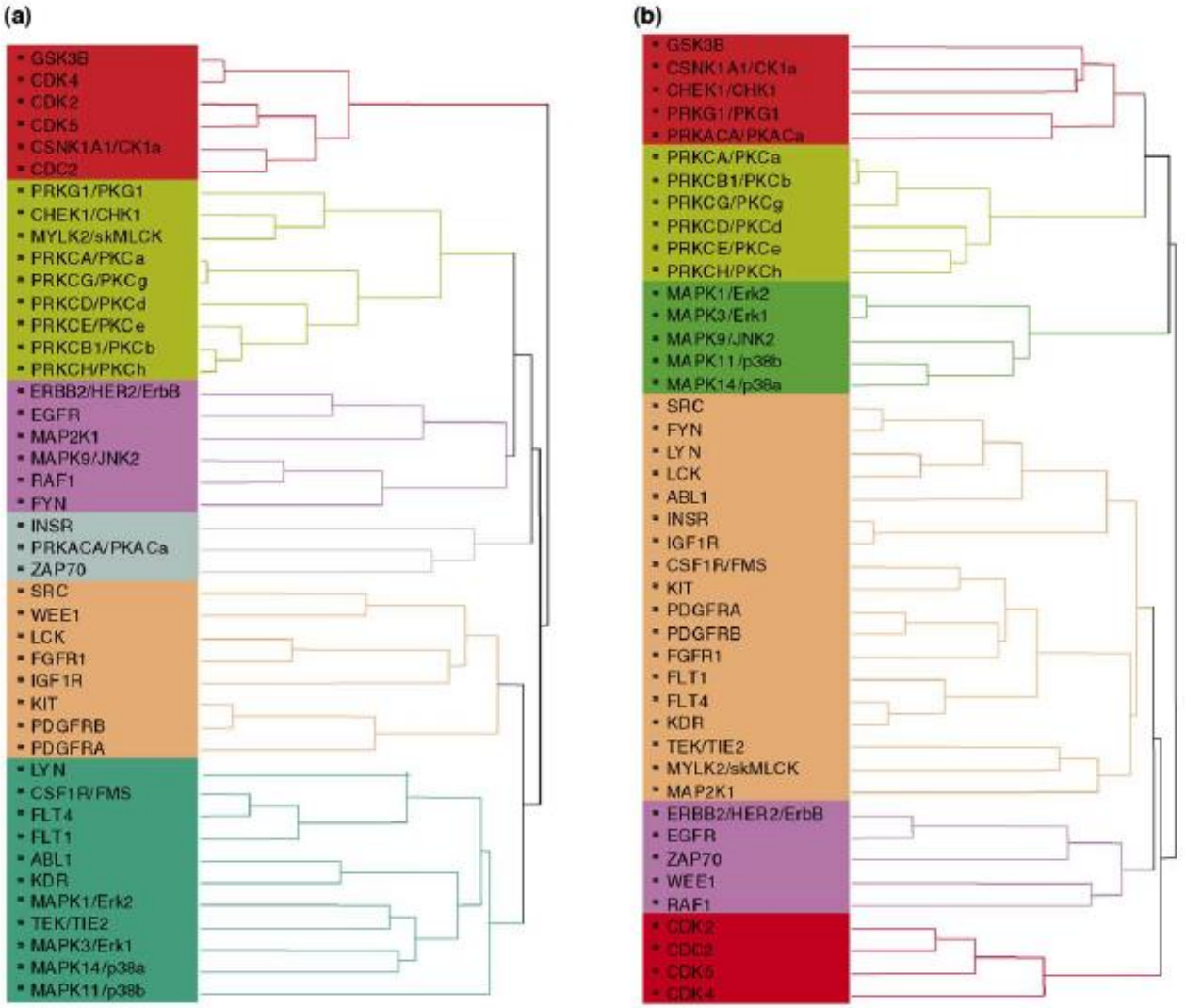


Njaoamine F
Source: Neopetrosia
Biological Activity: Cytotoxic

How?

I. identification of all members of a gene family
II. classification into subfamilies
III. revelation of common elements and patterns in the sequence and tertiary structures

Classification of protein kinases:
a) structure-activity relationship (SAR), b) conventional phylogenetic approach



Classification of proteins

- Conventional phylogenetic

  WHOLE STRUCTURE

- Chemogenomic

  SMALL-MOLECULE BINDING SITES

  (only a part of the enzyme structure, most commonly in active site of the enzyme)

Example

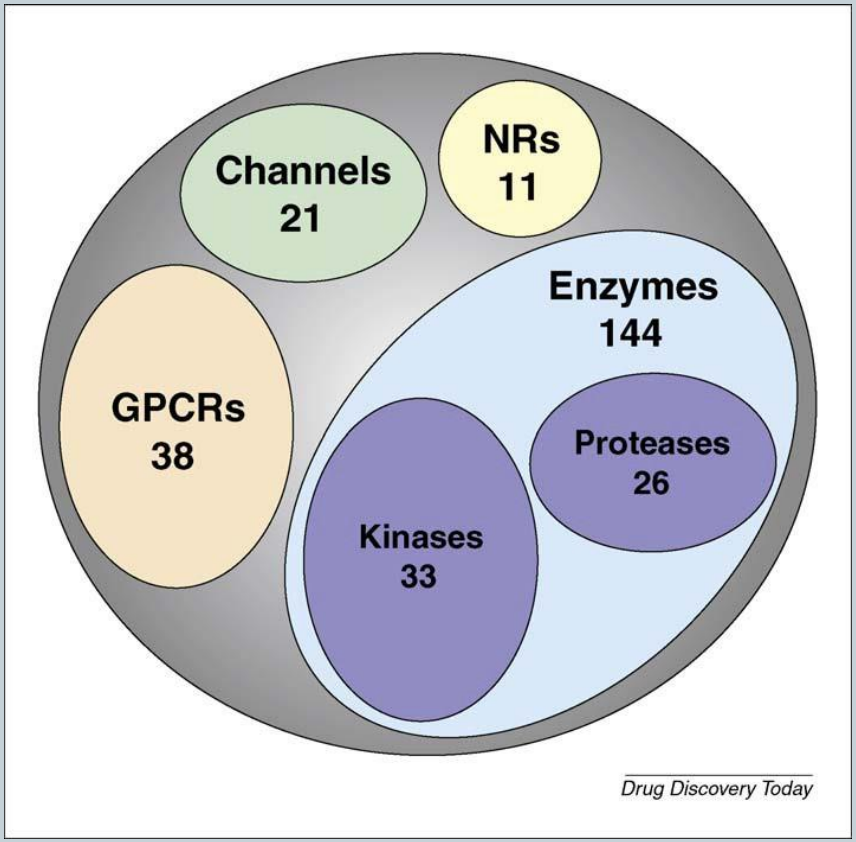
CHEMOGENOMIC APPROACH IN CARDIOVASCULAR DISEASES

1. Identification of target structures associated with cardiovascular diseases (literature research)
   - There were identified many proteins associated with cardiovascular system (233)
   - There were prepared a hundreds of small molecules (potential drugs) with proven aktivity on CVS (44 032)

Example

2. Organisation of cardiovascular targets in protein families
   - GPCR (G-related couple proteins)
   - Enzyme
   - Kinase
   - Proteinase
   - nuclear receptor
   - catalytic receptor
   - ion channel
   - Transporter
   - Other protein

Complication: alternative nomenclature of proteins



Example

3. The establishment of knowledge base of the cardiovascular target space
   - Determining the level of applicability of structure-based methods for *in silico* target profiling
   - Is the structure of targets known?
   - If it is – is there any relationship, similarity?
   - Which belong to the *Homo sapiens*?

Complication: there can be used only proteins with known structure (at least one characteristic representative of the family).

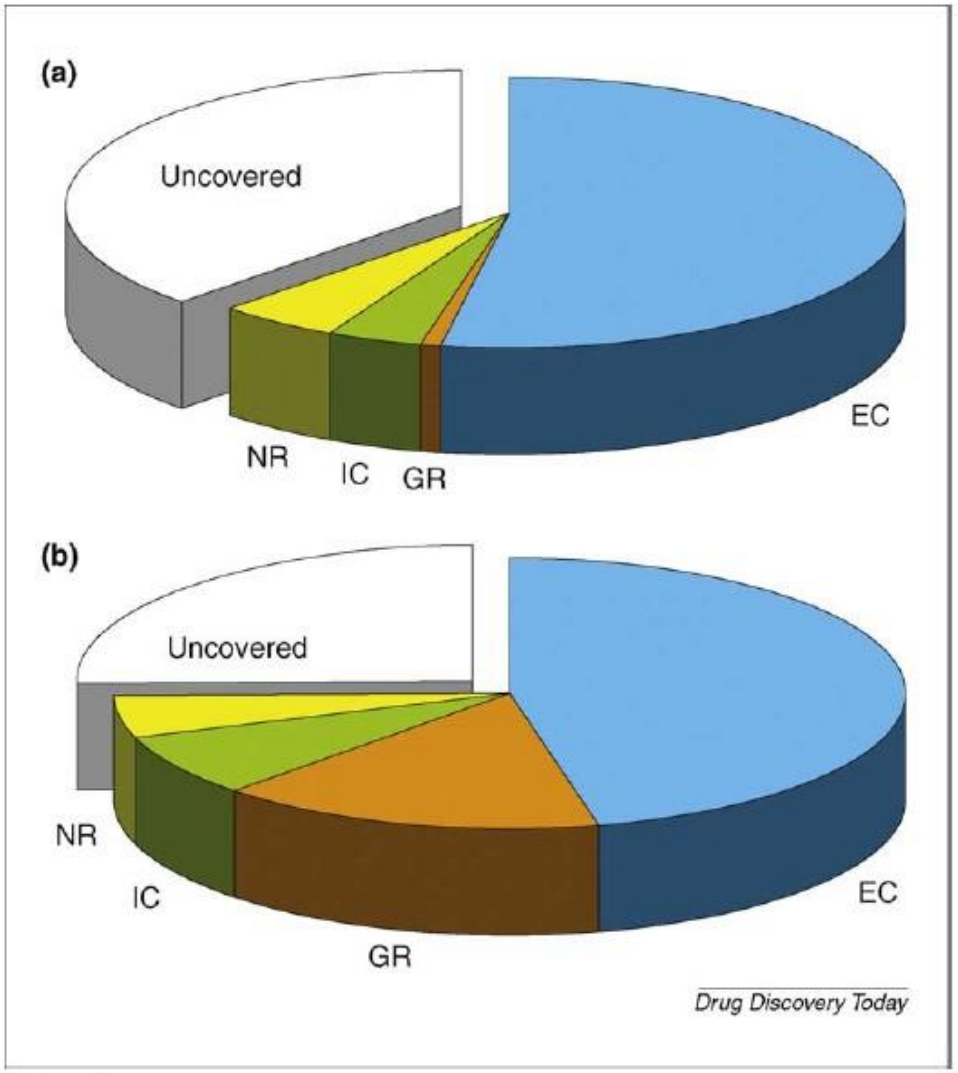


FIGURE 2

Structural and chemical coverage in cardiovascular target space. (a) Distribution of targets for which at least one representative structure exists in the Protein Data Bank and (b) distribution of targets for which at least one bioactive ligand is present in the annotated chemical libraries considered. EC: enzymes; GR: GPCRs; IC: ion channels; NR: nuclear receptors.

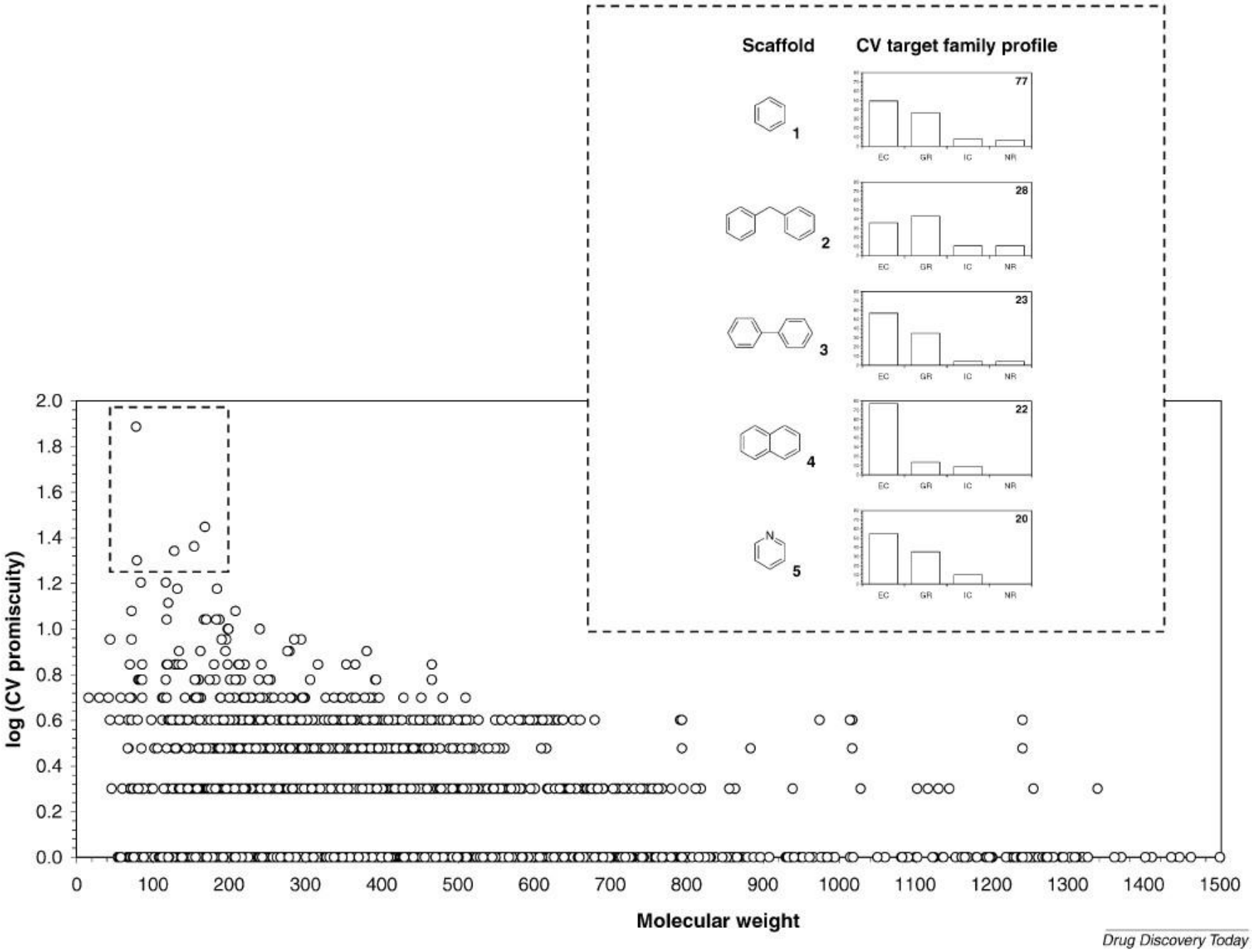
Example

5. Data from chemical libraries
   - Ligands with pharmacological potency at (at least one of) cardiovascular target structure

6. Identification of atomic frameworks or scaffolds

7. Synthesis

8. Biological evaluation



Drug Discovery Today

THANK YOU

FOR YOUR ATTENTION

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