



Palestra Científica

Antibióticos – Uma luta sem fim



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Importância dos PNs para Síntese de Novos Fármacos. Busca por espaços químicos ainda inexplorados. BIOS (Biology Oriented Synthesis)

**Desenvolvimento de novos agentes antimicrobianos – BIOLAB
IQ/UFRGS**

PNs como candidatos a Drogas



Produtos naturais (PNs) são entidades químicas produzidas por organismos vivos.

São metabólitos secundários (compostos não essenciais para a sobrevivência do hospedeiro).

Apresentam especial interesse no desenvolvimento de drogas.

São tipicamente produzidos por organismos vivos: bactérias, plantas ou invertebrados marinhos. Geralmente utilizados como “defensores químicos” de defesa ou frente a predadores.

PNs como Drogas

2000 a 2006: 26 PNs derivados de plantas estavam em algum estágio clínico de desenvolvimento de drogas.

2005: drogas derivadas de PNs registraram U\$ 18 bilhões em vendas.

A diversidade de PNs está expandindo continuamente sendo recentemente incluídas moléculas originadas em águas profundas e oceanos congelados.

PNs apresentam grande impacto na descoberta e desenvolvimento de antibióticos e drogas para o tratamento de cancer.

Protótipos a Partir da Natureza

Extrato de Plantas

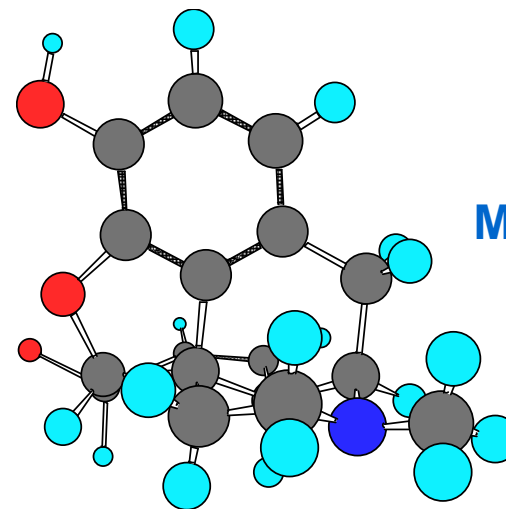


Flor da papola

Algafan® (propoxifeno)

Efeito analgésico

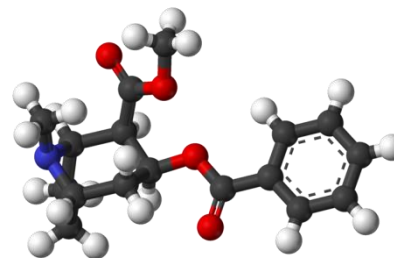
Grande dependência química



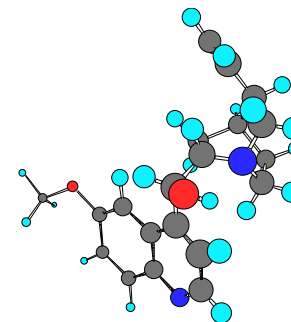
Protótipos a Partir da Natureza

Extrato de Plantas

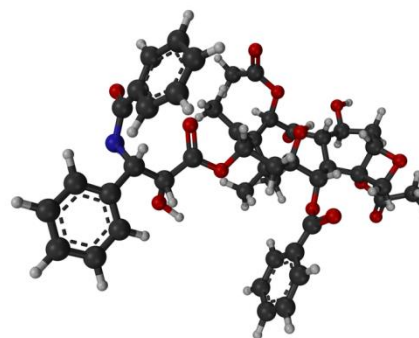
- **COCA** - Cocaina



- **CINCHONA** - Quinina



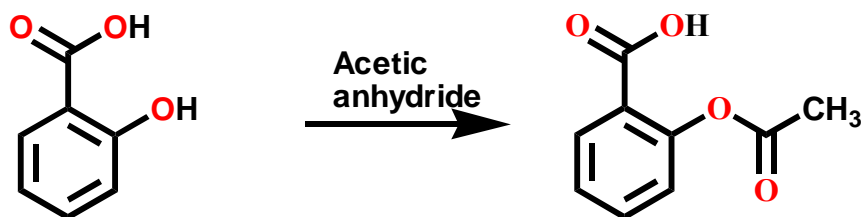
- **Teixo** - Taxol



Protótipos a Partir da Natureza

Extrato de Plantas – Semi síntese e síntese

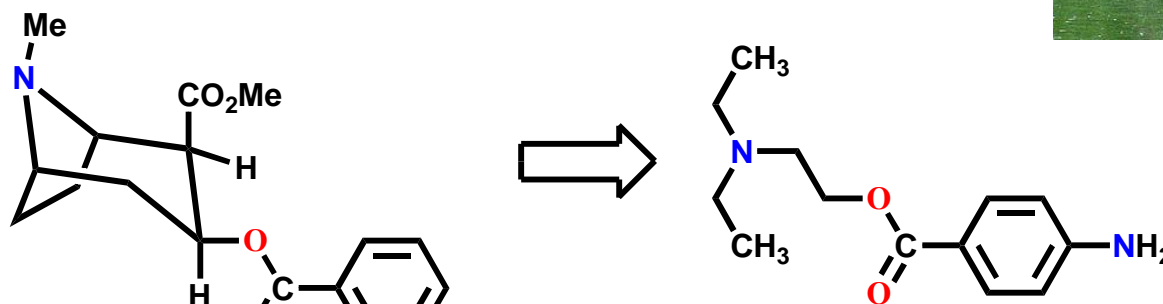
SALGUEIRO - ácido salicílico



Aspirina



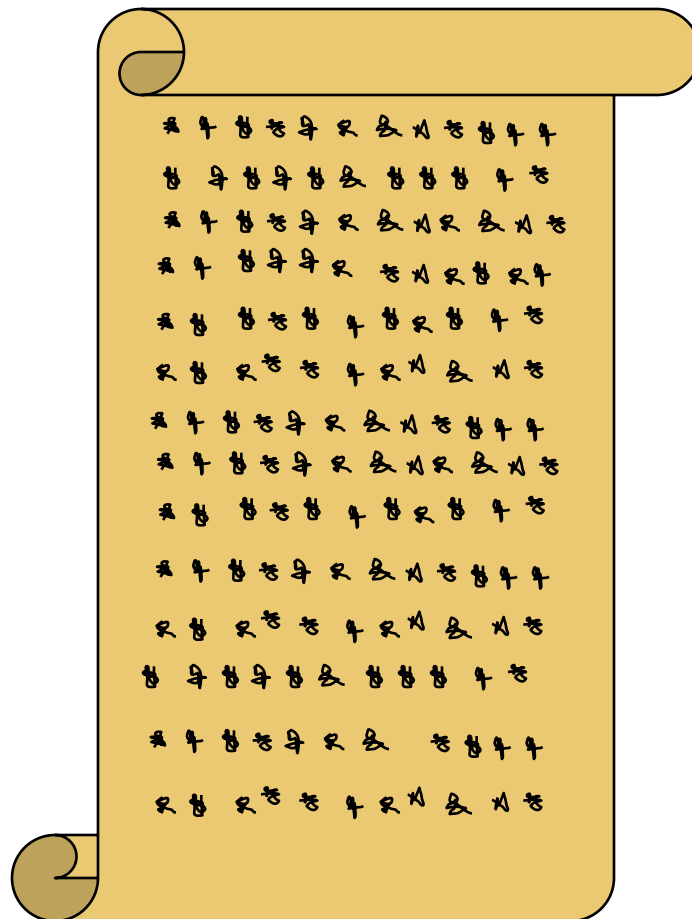
COCA - COCAINE



Procaina

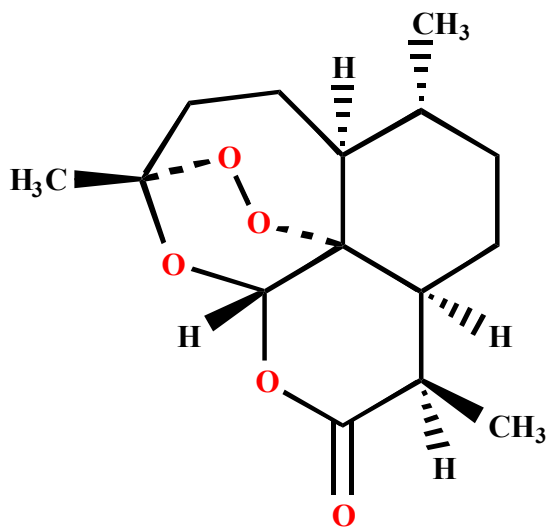
Protótipos a Partir da Natureza

PLANTAS E MEDICINA MILENAR

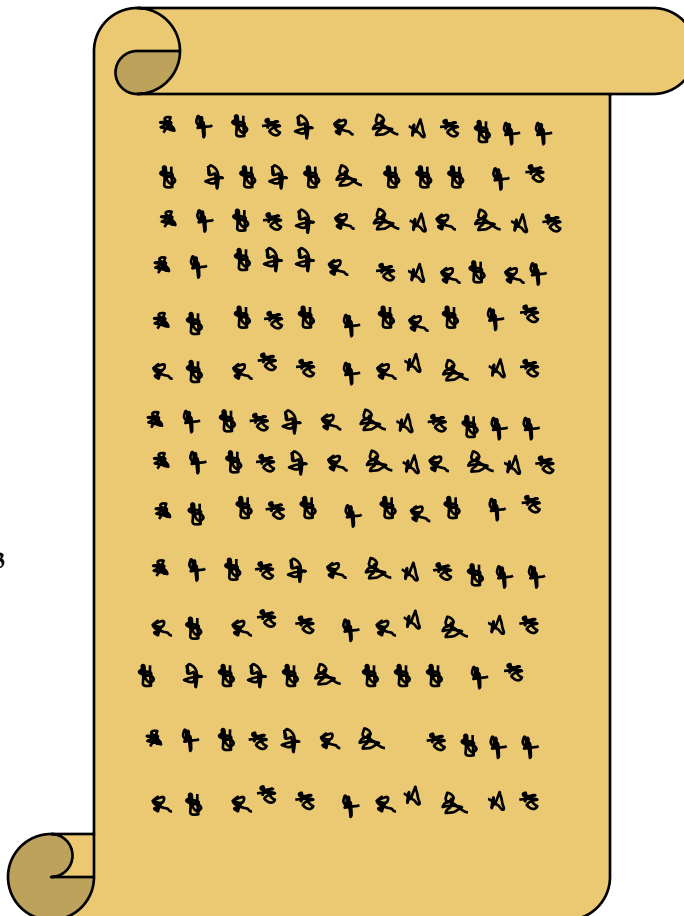


Protótipos a Partir da Natureza

PLANTS AND ANCIENT RECORDS



ARTEMISININA
(Malária)

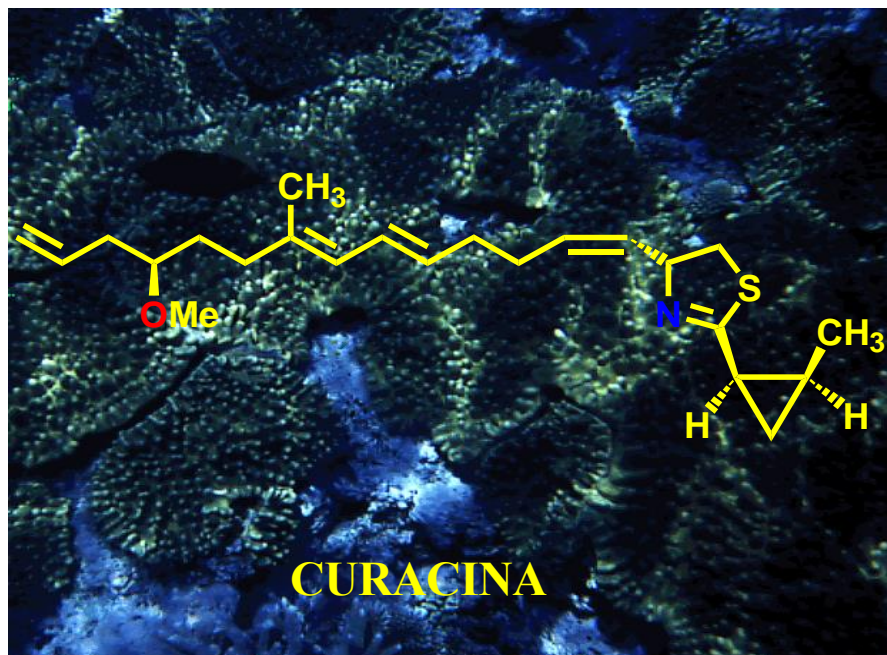


Medicina Chinesa



Protótipos a Partir da Natureza

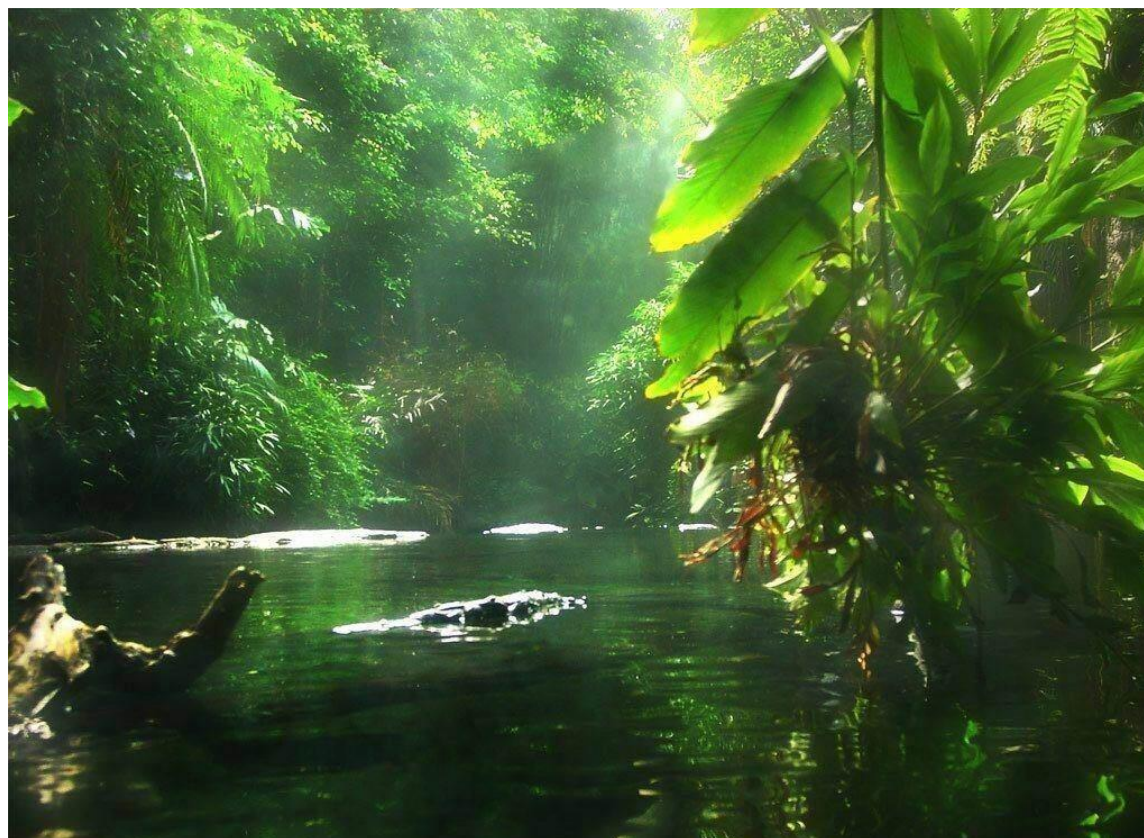
QUÍMICA MEDICINAL MARINHA DE CORAIS



Interage com tubulinas
 Baixa solubilidade oral

Protótipos a Partir da Natureza

Florestas – fonte inimaginável de PNs interessantes



Será que nós brasileiros conseguiremos explorá-la?

Protótipos a Partir da Natureza

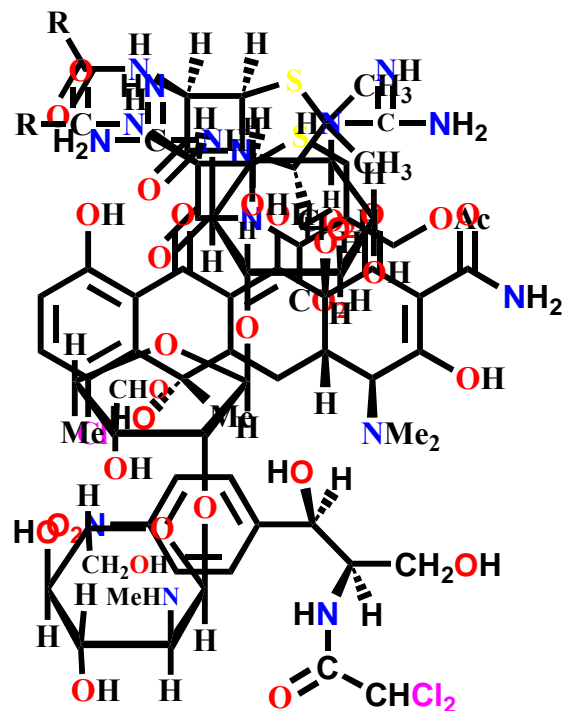
MICRO-ORGANISMS



Protótipos a Partir da Natureza

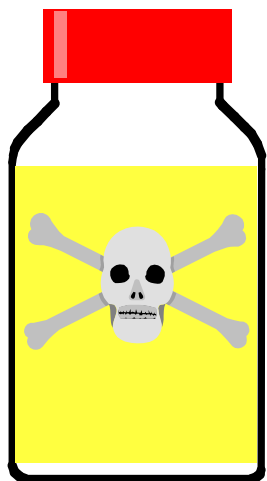
MICRO-ORGANISMS

- **PENICILINA**
- **CEFALOSPORINAS**
- **TETRACICLINAS**
- **ESTREPTOMICINA**
- **CLORANFENICOL**

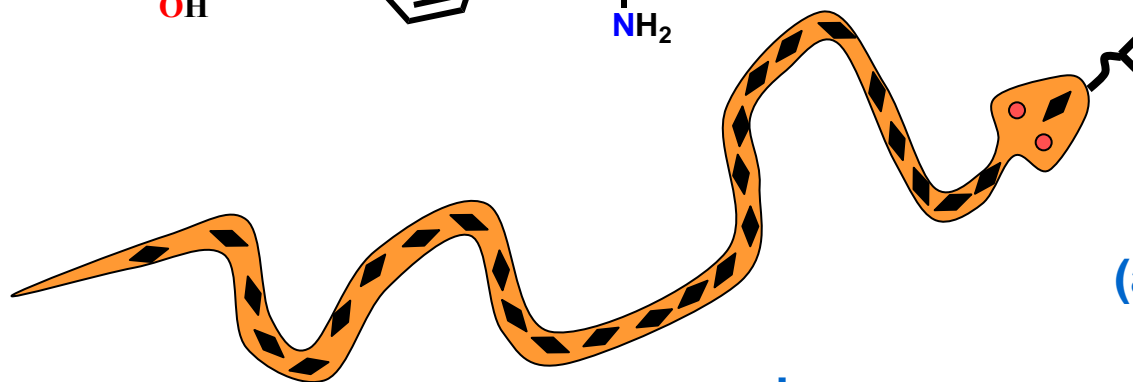
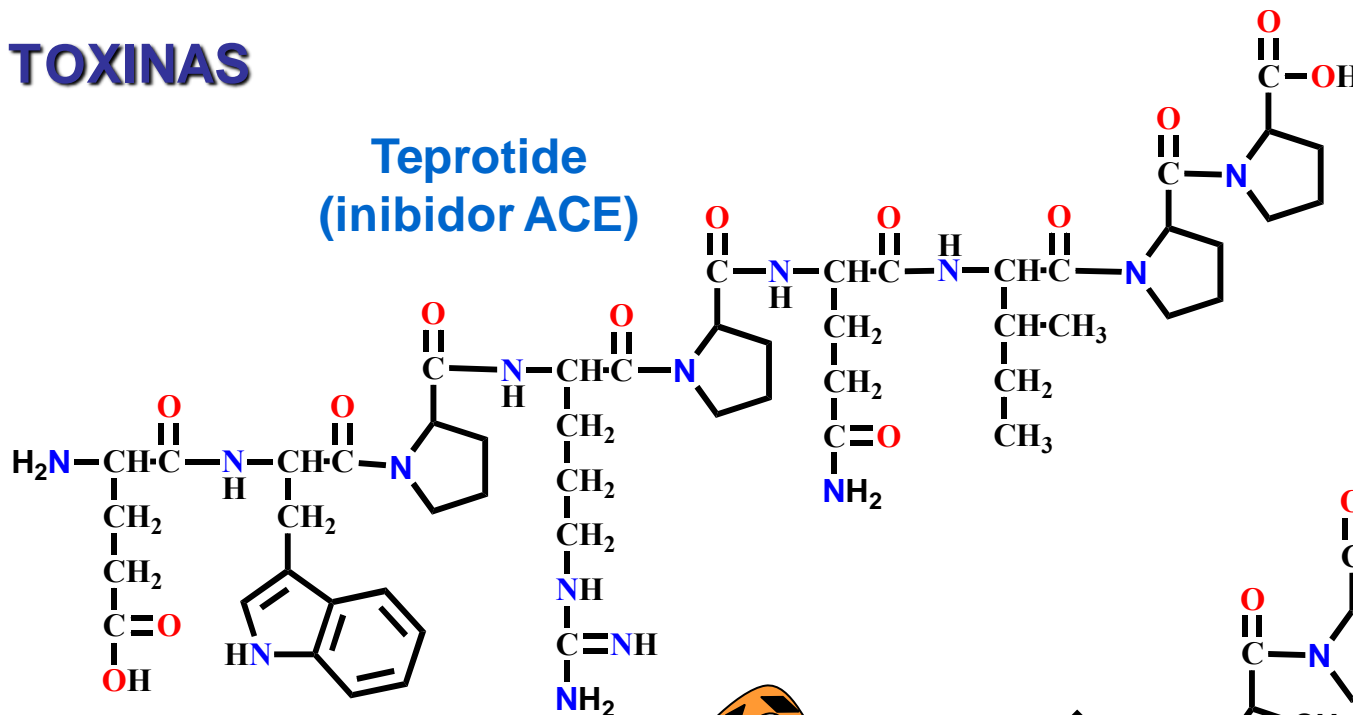


Protótipos a Partir da Natureza

VENONOS E TOXINAS

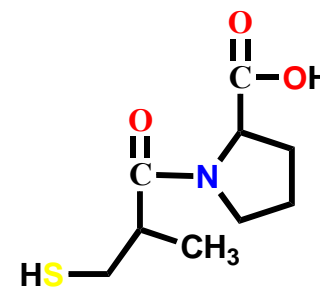


Teprotide
(inibidor ACE)



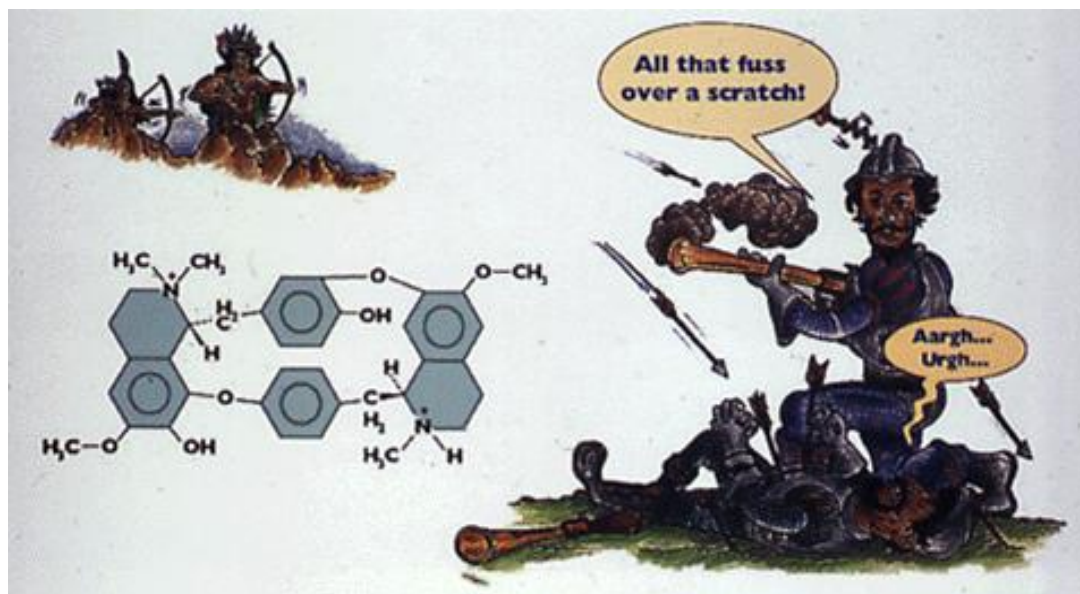
Jararaca

Captopril
(anti-hipertensivo)



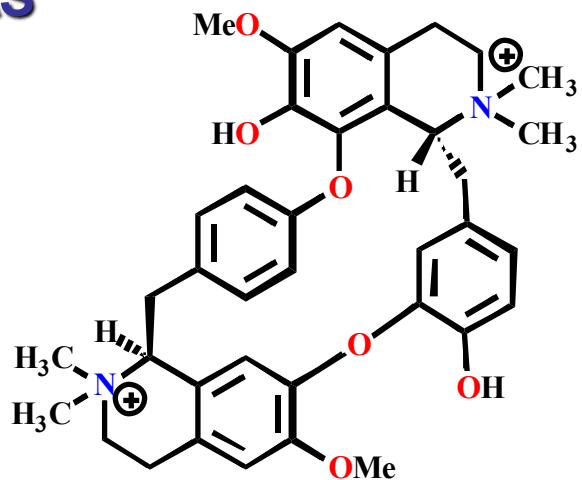
Protótipos a Partir da Natureza

VENONOS E TOXINAS



Protótipos a Partir da Natureza

VENONOS E TOXINAS

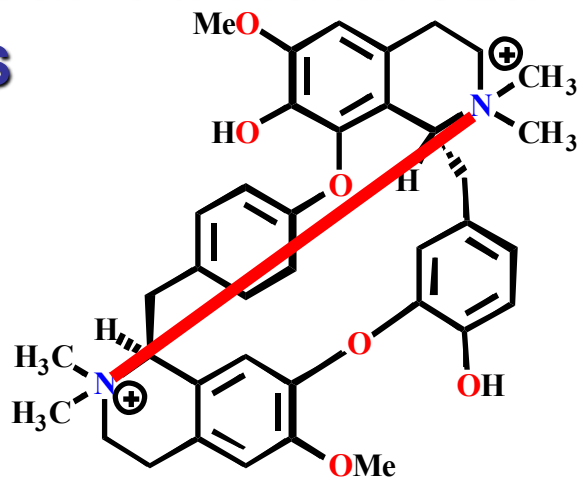


Tubocurarina
(curaro)

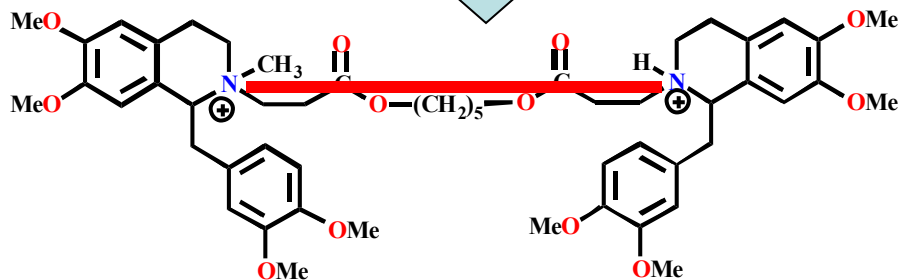


Protótipos a Partir da Natureza

VENOMS AND TOXINS



Tubocurarine
(from curare)

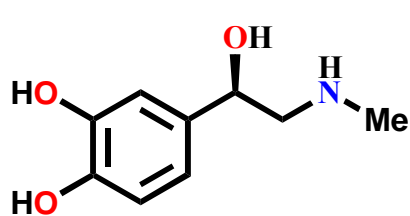


Atracurium
(Neuromuscular blocker)

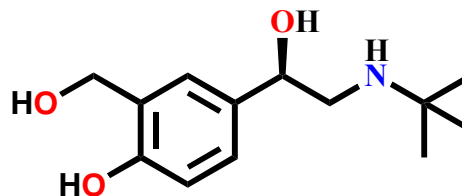
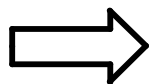
Protótipos a Partir da Natureza

ENDOGENOUS COMPOUNDS

Compostos idealizados a partir de Ligantes naturais de receptores:

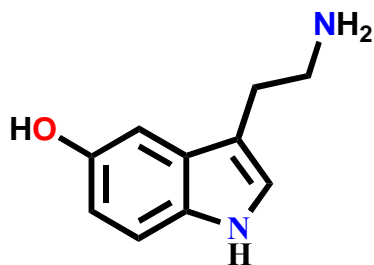


ADRENALINE

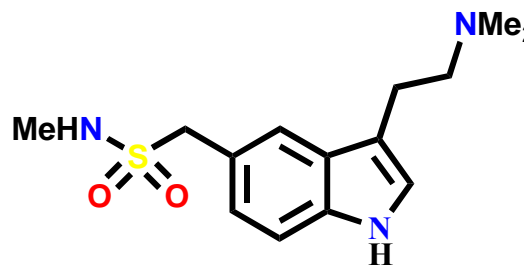
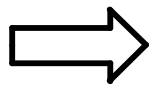


SALBUTAMOL

Agonist



5-HYDROXYTRYPTAMINE



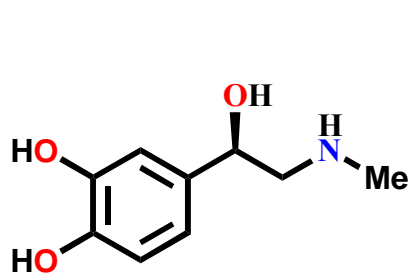
SUMATRIPTAN

Agonist

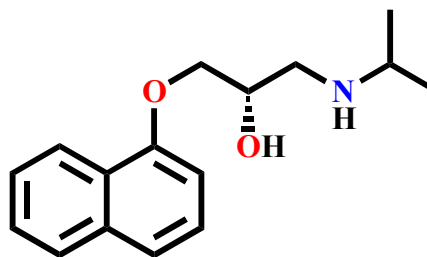
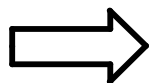
Protótipos a Partir da Natureza

ENDOGENOUS COMPOUNDS

Compostos idealizados a partir de Ligantes naturais de receptores:

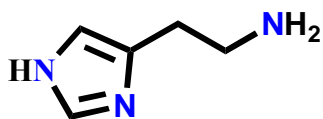


ADRENALINE

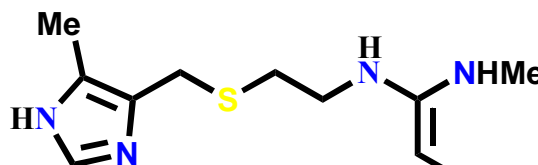
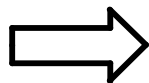


PROPRANOLOL

Antagonist



HISTAMINE



CIMETIDINE

Antagonist

PNs como Drogas

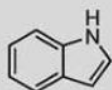
Apresentam atividade frente a múltiplos alvos proteicos...Portanto, são consideradas “**Estruturas privilegiadas**” que evoluíram na natureza produzindo essas propriedades. Assim, são scaffolds pré-validados (evolução natural) que podem ser utilizados como ponto de partida para o planejamento de bibliotecas de compostos.

Privileged Scaffolds

(exemplos – Produtos naturais)

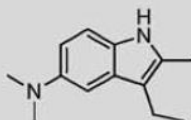
Privileged Scaffold

Structures



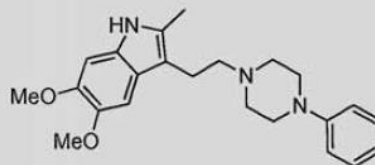
Indole

Drugs



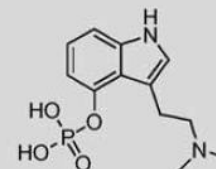
Medmain

Therap. Cat: Serotonin inhibitor



Oxypertine

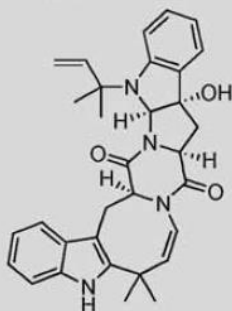
Therap. Cat: Antidepressant



Psilocybin

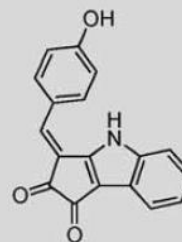
Therap. Cat: Psychomimetic

Natural Products



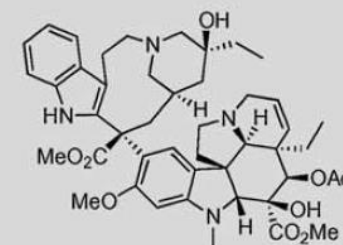
Okaramine N

Source: *Penicillium simplicissimum*
Biological Activity: Insecticidal activity



Nostodione A

Source: The terrestrial blue-green algae
Nostocommune
Biological Activity: Mitotic spindle poison



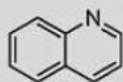
Vinblastine

Source: Leaves of Madagascar periwinkle plant (*Cantharanthus roseus*)
Biological Activity: Anticancer agent; causes apoptosis by stopping spindle formation during mitosis

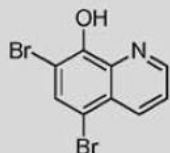
Privileged Scaffolds

(exemplos – Produtos naturais)

Drugs

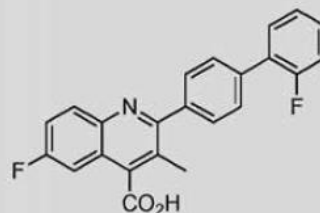


Quinoline



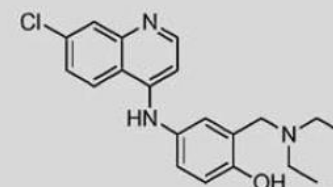
Broxyquinoline

Therap Cat: Antiseptic; disinfectant



Brequinar

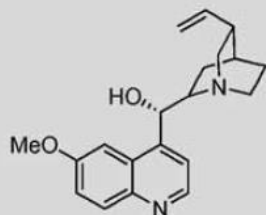
Therap Cat: Immunosuppressant



Amodiaquin

Therap Cat: Antimalarial

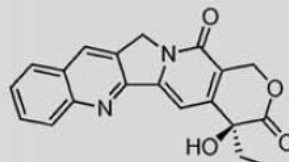
Natural Products



Quinine

Source: Quina Bark

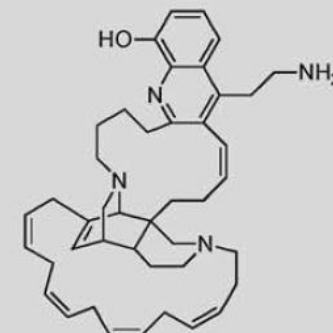
Biological Activity: Anti-malarial



Camptothecin

Source: The Chinese tree *Camptotheca acuminata* Decne

Biological Activity: Anti-cancer activity



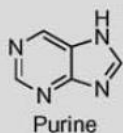
Njaoamine F

Source: Neopetrosia

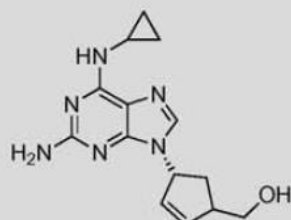
Biological Activity: Cytotoxic

Privileged Scaffolds

(exemplos – Produtos naturais)

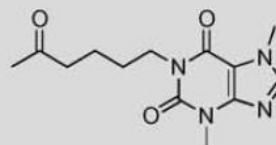


Drugs



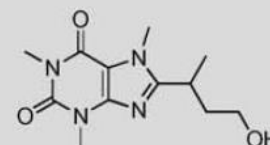
Abacavir

Therap. Cat: Antiviral (HIV)



Pentoxifylline

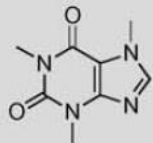
Therap. Cat: Hemorheologic agent



Cafaminol

Therap. Cat: Decongestant (nasal)

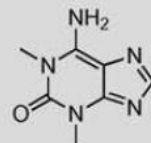
Natural Products



Caffeine

Source: Coffee beans, tea leaves

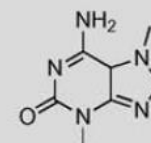
Biological Activity: Stimulant



1,3 Dimethylisoguanine

Source: Amphimedon viridis

Biological Activity: Cytotoxic to human ovarian cancer cells



3,7 Dimethylisoguanine

Source: Agelas longissima

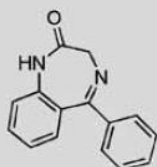
Biological Activity: Antibacterial

Privileged Scaffolds

(exemplos – Produtos sintéticos)

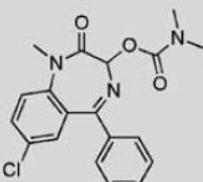
Examples of privileged scaffolds found primarily in drugs

Privileged Scaffold

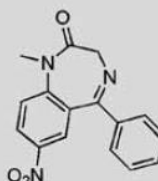


Benzodiazepine

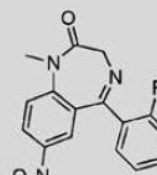
Structures



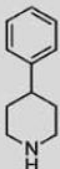
Camazepam
Therap. Cat: Anxiolytic



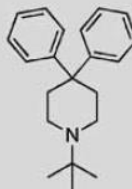
Nimetazepam
Therap. Cat: Sedative, hypnotic



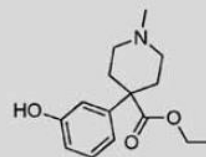
Flunitrazepam
Therap. Cat: Hypnotic



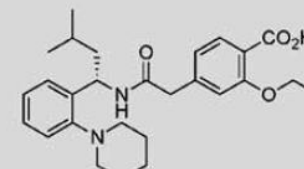
Arylpiperidine



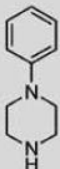
Butdipine
Therap. Cat: Antiparkinsonian



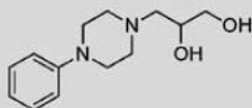
Hydroxypethidine
Therap. Cat: Analgesic (narcotic)



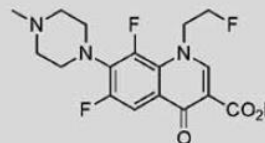
Repaglinide
Therap. Cat: Antidiabetic



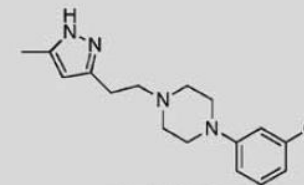
Arylpiperazine



Dropropizine
Therap. Cat: Antitussive



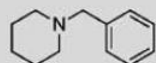
Fleroxacin
Therap. Cat: Antibacterial



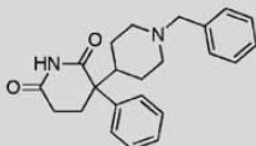
Mepiprazole
Therap. Cat: Tranquillizer

Privileged Scaffolds

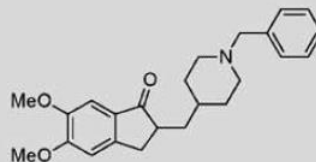
(exemplos – Produtos sintéticos)



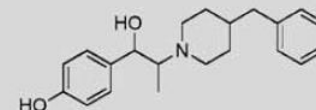
Benzylpiperidine



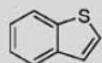
Benzetimide
Therap. Cat: Antiparkinsonian



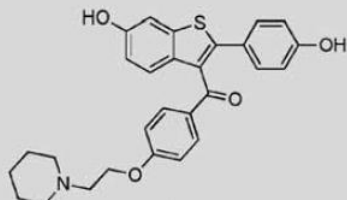
Donepezil
Therap. Cat: Nootropic



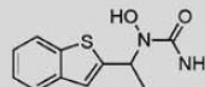
Ifenprodil
Therap. Cat: Vasodilator
(cerebral and peripheral)



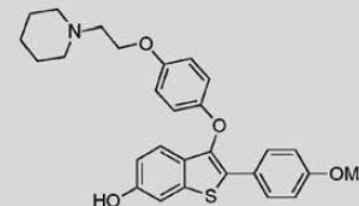
Benzothiophene



Raloxifene
Therap. Cat: Antiosteoporotic



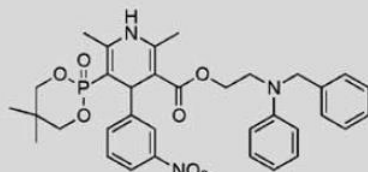
Zileuton
Therap. Cat: Antiasthmatic



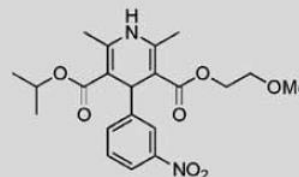
Arzoxifene
Therap. Cat: Antineoplastic (hormonal)



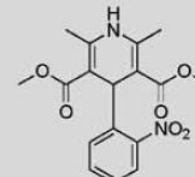
Dihydropyridines



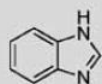
Efonidipine
Therap. Cat: Antihypertensive



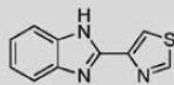
Nimodipine
Therap. Cat: Vasodilator (cerebral)



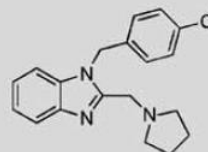
Nifedipine
Therap. Cat: Antianginal;
antihypertensive



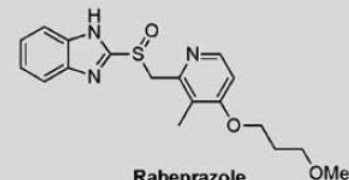
Benzimidazole



Thiabendazole
Therap. Cat: Anthelmintic



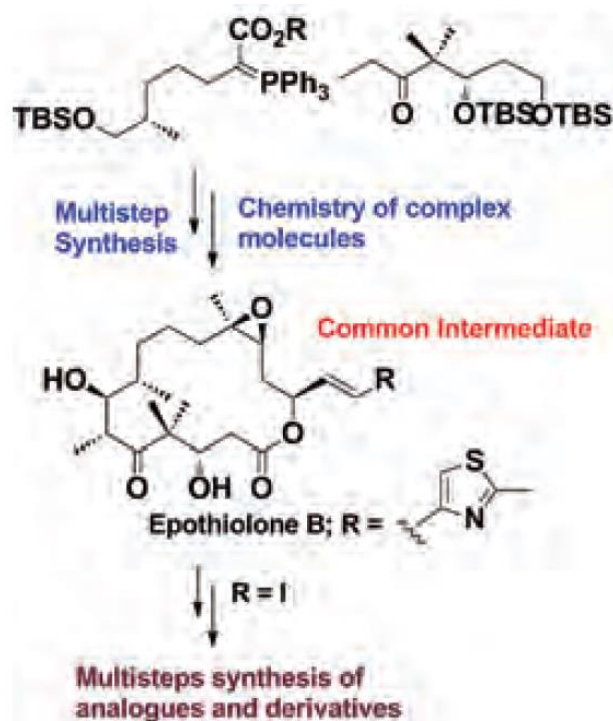
Clemizole
Therap. Cat: Antihistaminic



Rabeprazole
Therap. Cat: Antilucerative

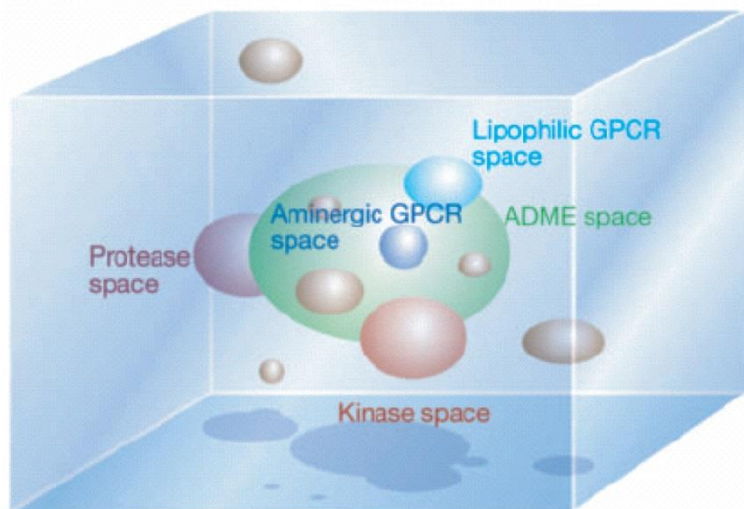
Problemas PNs

(Química Medicinal)



- PNs são geralmente muito complexos para serem sintetizados.
- Estruturas muito grandes em termos de Química Medicinal.
- Geralmente não são disponíveis em quantidades suficientes a partir de fontes naturais para modificações (preparação de análogos e derivados).

Espaço Químico



Espaço Químico (azul claro) e espaços discretos ocupados por compostos com afinidade específica com biomoléculas: major gene families (brown); specific gene families: proteases (purple), lipophilic GPCRs (blue) and kinases (red).

Verde: espaço ocupado por moléculas contendo propriedades ADME privilegiadas.



Richard Lipinsky

Drug-likeness

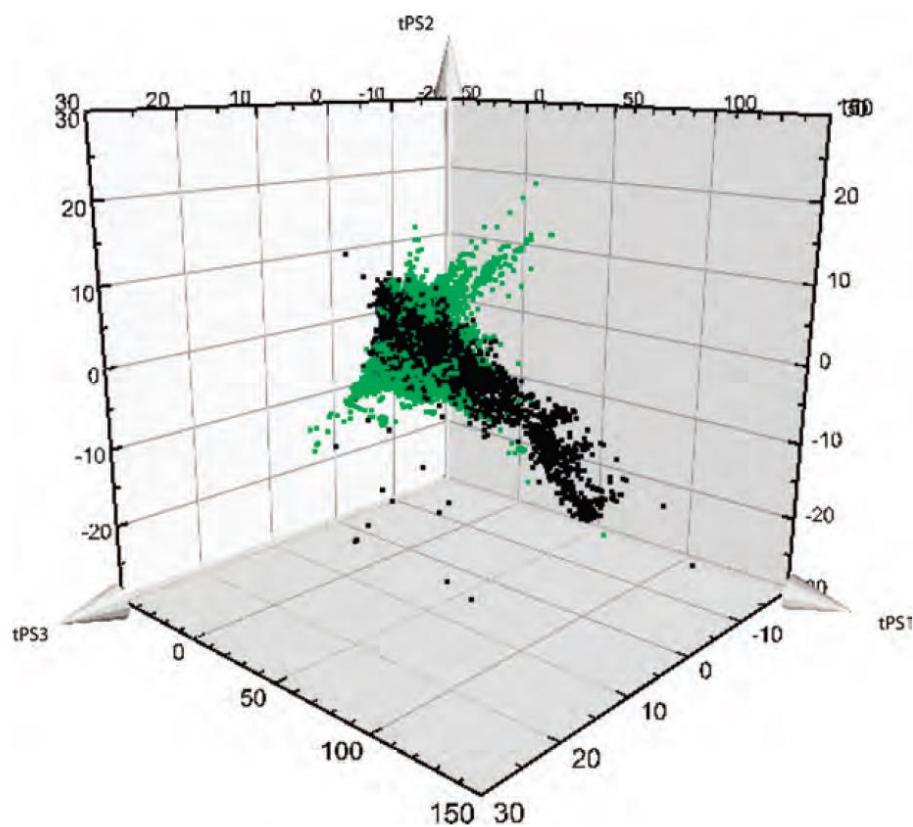
Rule of Five

$M_r < 500$
 < 5 H-Bond Donor
 < 10 H-Bond Acceptor
 $cLog P < 5$

Modified Rule of Five

< 10 Rotatable Bonds
 $PSA < 140 \text{ \AA}^2$ [high %F]
 $PSA < 90 \text{ \AA}^2$ [high %F & BBB]
 < 12 H-Bond Donor & Acceptor

Espaço Químico PNs vs Compostos Bioativos



**Preto: Espaço Químico de
compostos bioativos em
Química Medicinal (WOMBAT)**

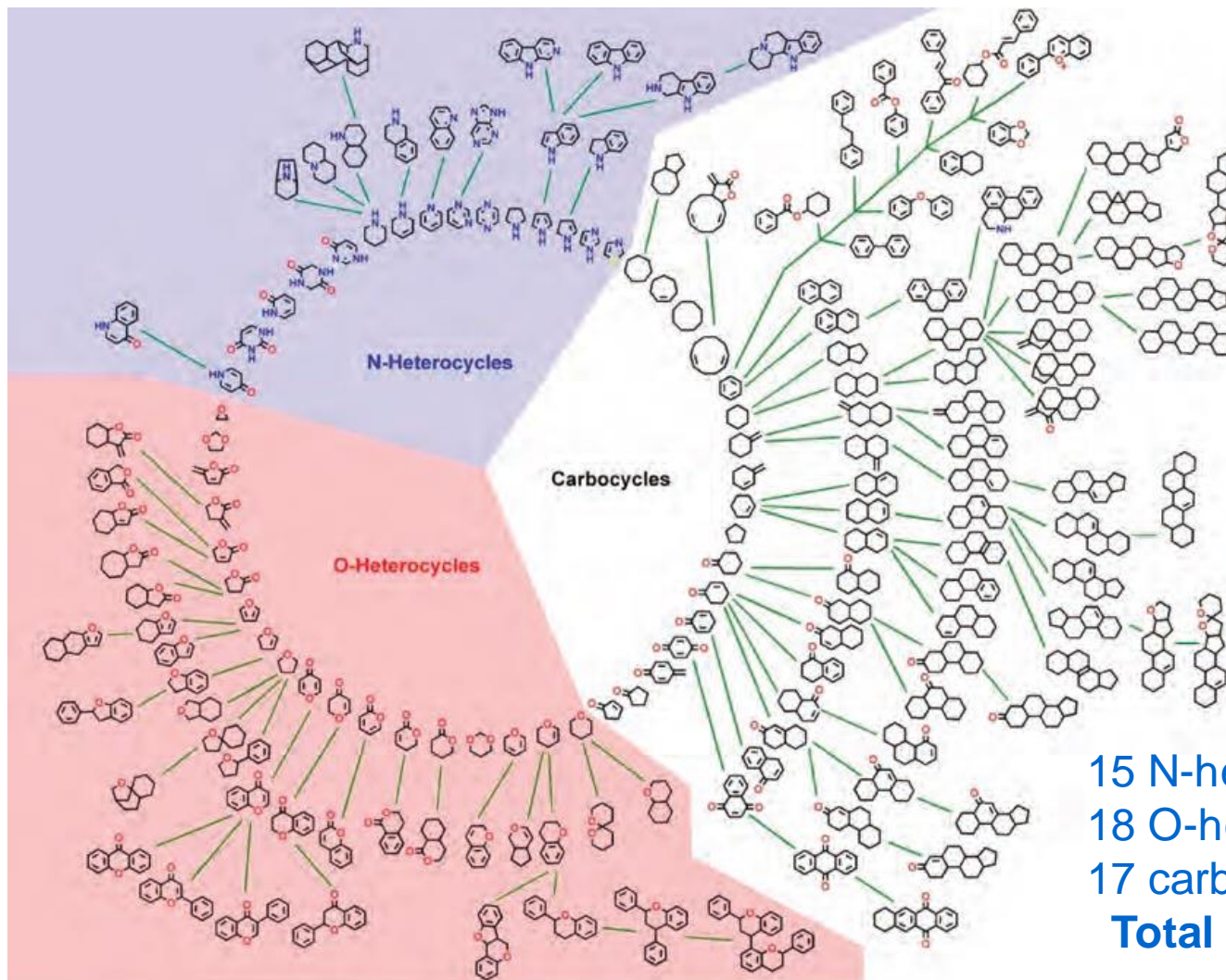
Verde: Espaço Químico de PN

Como Achar a Agulha no Palheiro?

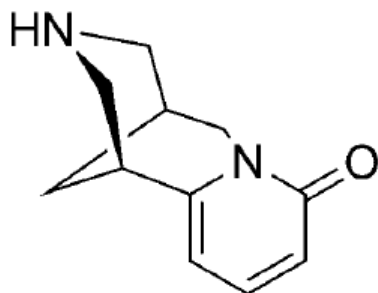


Árvore de Scaffolds - PNs

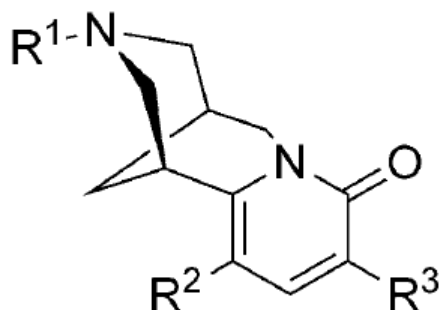
Classificação hierárquica baseada em Scaffolds de PNs (SCONP).



Coleções Derivadas de PNs



Cytisine



Scaffold idêntico ao scaffold do produto natural.

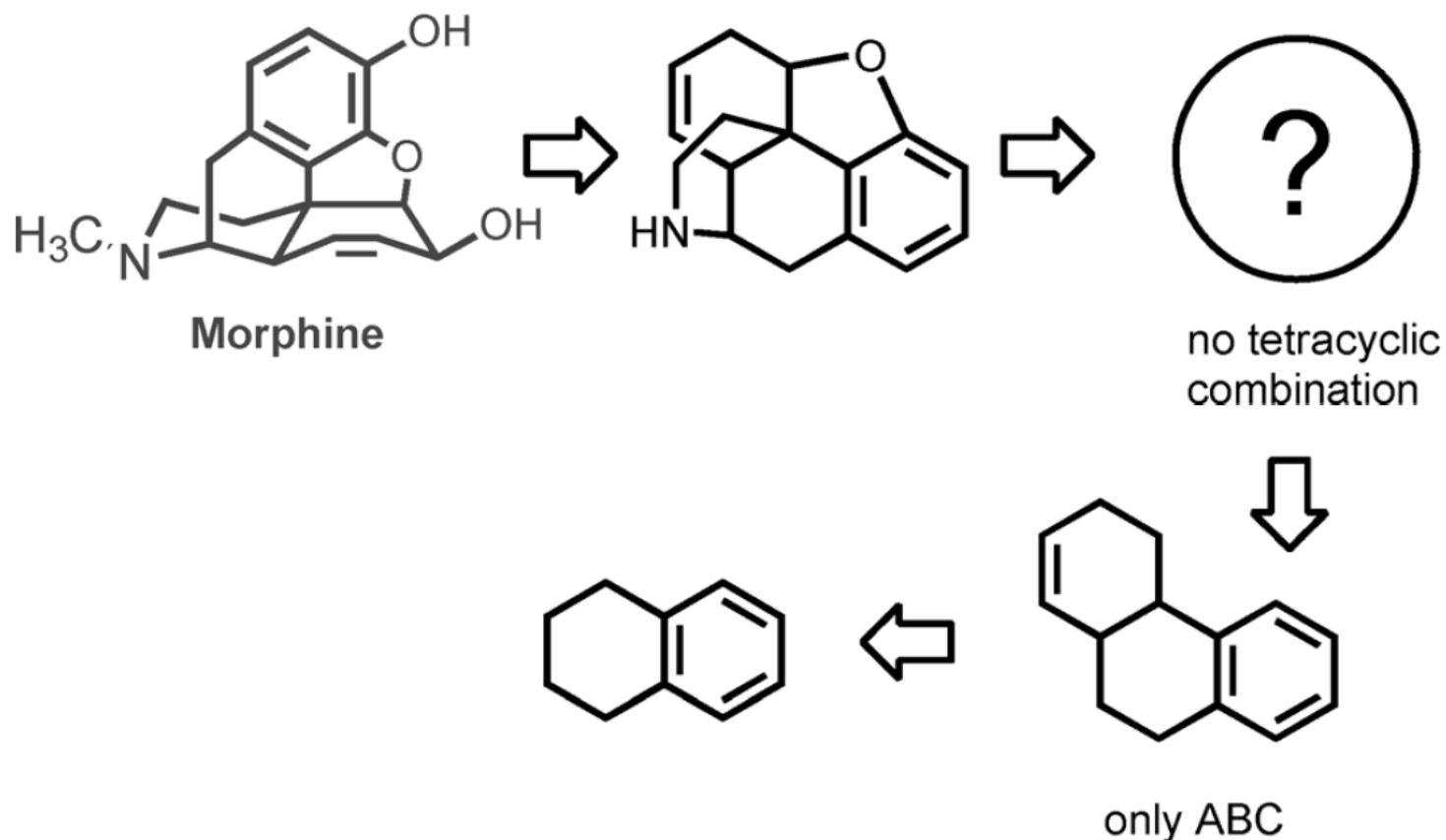
Scaffold é basicamente obtido pela desmonte do produto (natural síntese também possível).

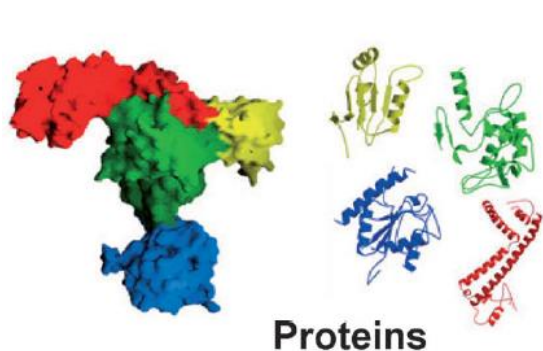
O padrão de substituição é determinado pela reatividade do scaffold presente na estrutura do PN.

Sem variação na estereoquímica.

Morfina

Classificação baseada em SCONP revela furos na deconvolução de PNs.
Nenhum PN tetracíclico derivado da morfina é conhecido e apenas 1 derivado tricíclico foi encontrado na natureza.

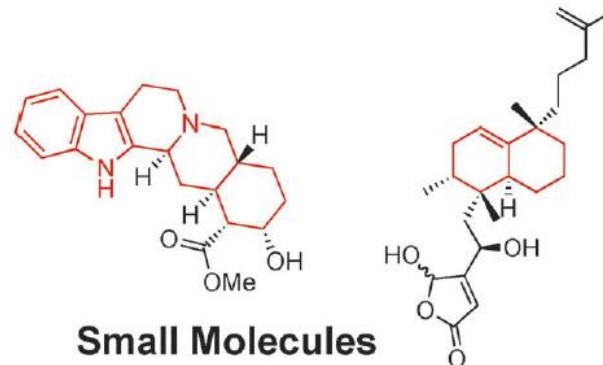




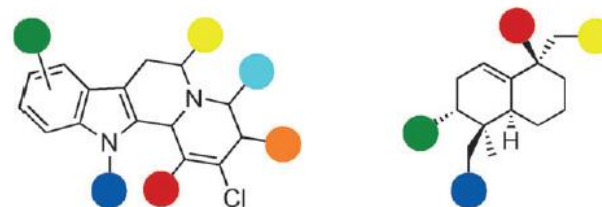
Limited number of fold types result in conserved shapes of ligand binding sites.

...AGHLAVRGA AKME...
 ...SGHLAVRGSARMD...
 ...WYANGPADYS...
 ...YYANGPAEWV...

Diverse amino acid sequences determine interaction patterns in ligand binding sites.

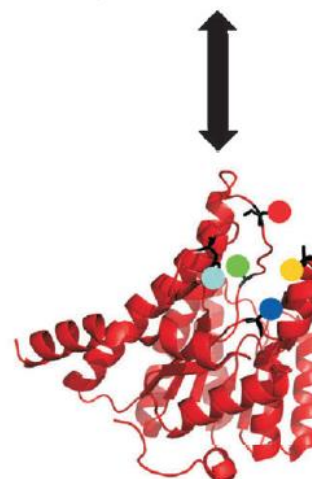


Limited number of scaffold classes result in conserved substituent orientation by ligand frameworks.



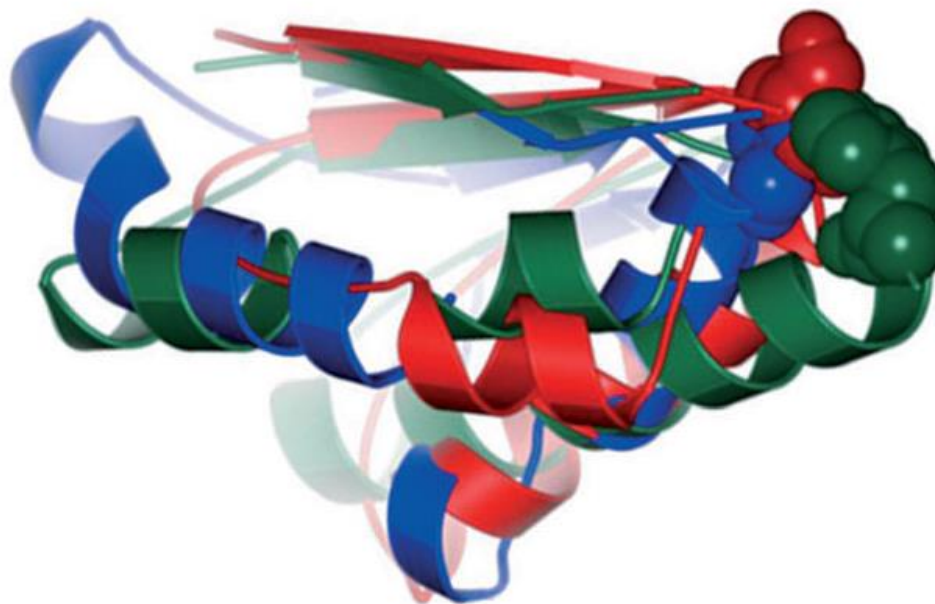
Diverse substituent patterns determine interaction patterns of individual ligands.

Agrupamento de estruturas proteicas por similaridade (PSSC)

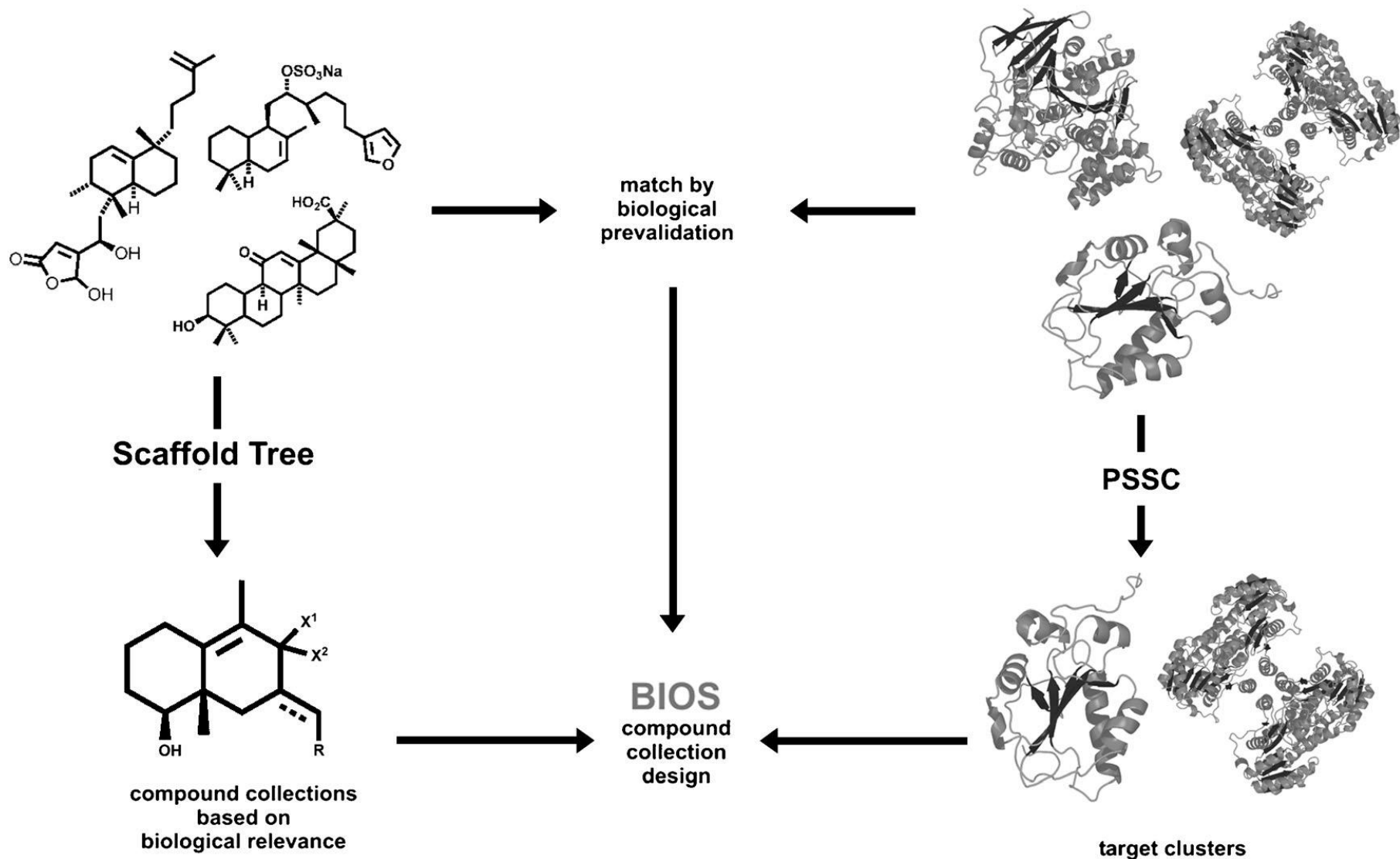


PSSC (Exemplo)

3 enzimas possuem < 10% de similaridade e não possuem relação mecanística.



Sítios catalíticos superpostos para **Cdc25A** (fosfatase- vermelho), **11 β HSD1** (metabismo glicose - verde) e **AChE** (azul). Principais resíduos catalíticos mostrando na representação de espaço preenchido **Cys-430** (**Cdc25A**), **Tyr-183** (**11 β HSD1**) e **Ser-200** (**AChE**).



Keywords:

- bioorganic chemistry ·
- chemoinformatics ·
- medicinal chemistry ·
- natural products ·
- synthesis design



Drug Candidates
Chemical Probes
New Targets

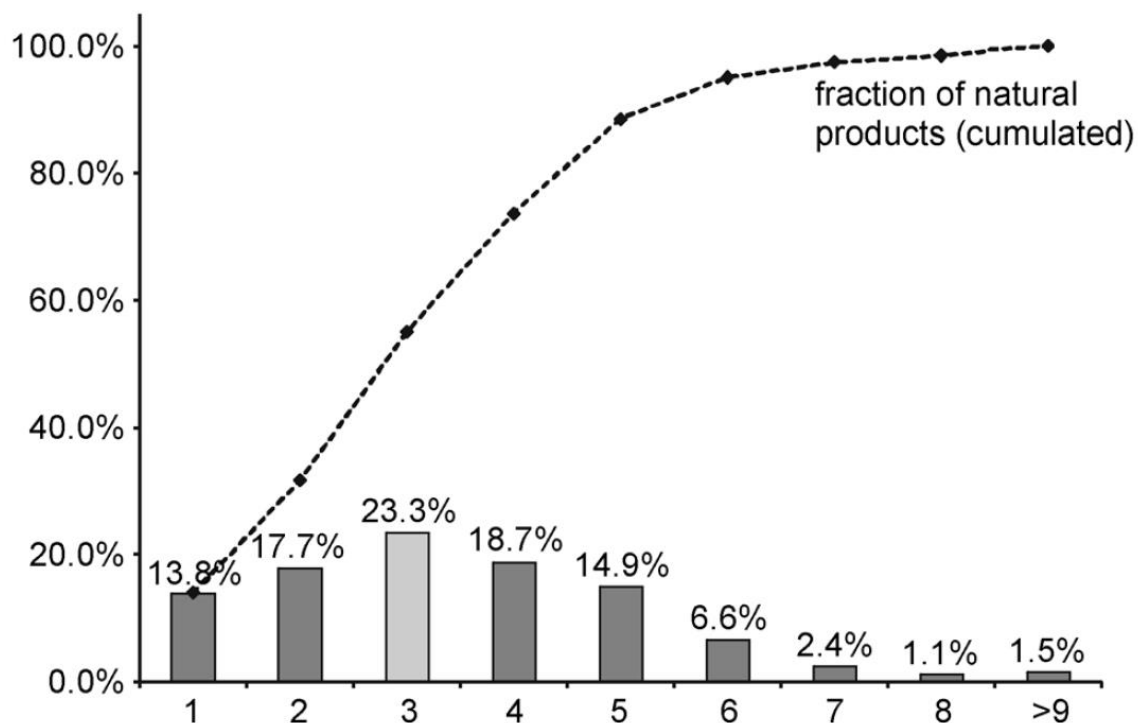
Angewandte
Chemie

10800 www.angewandte.org

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

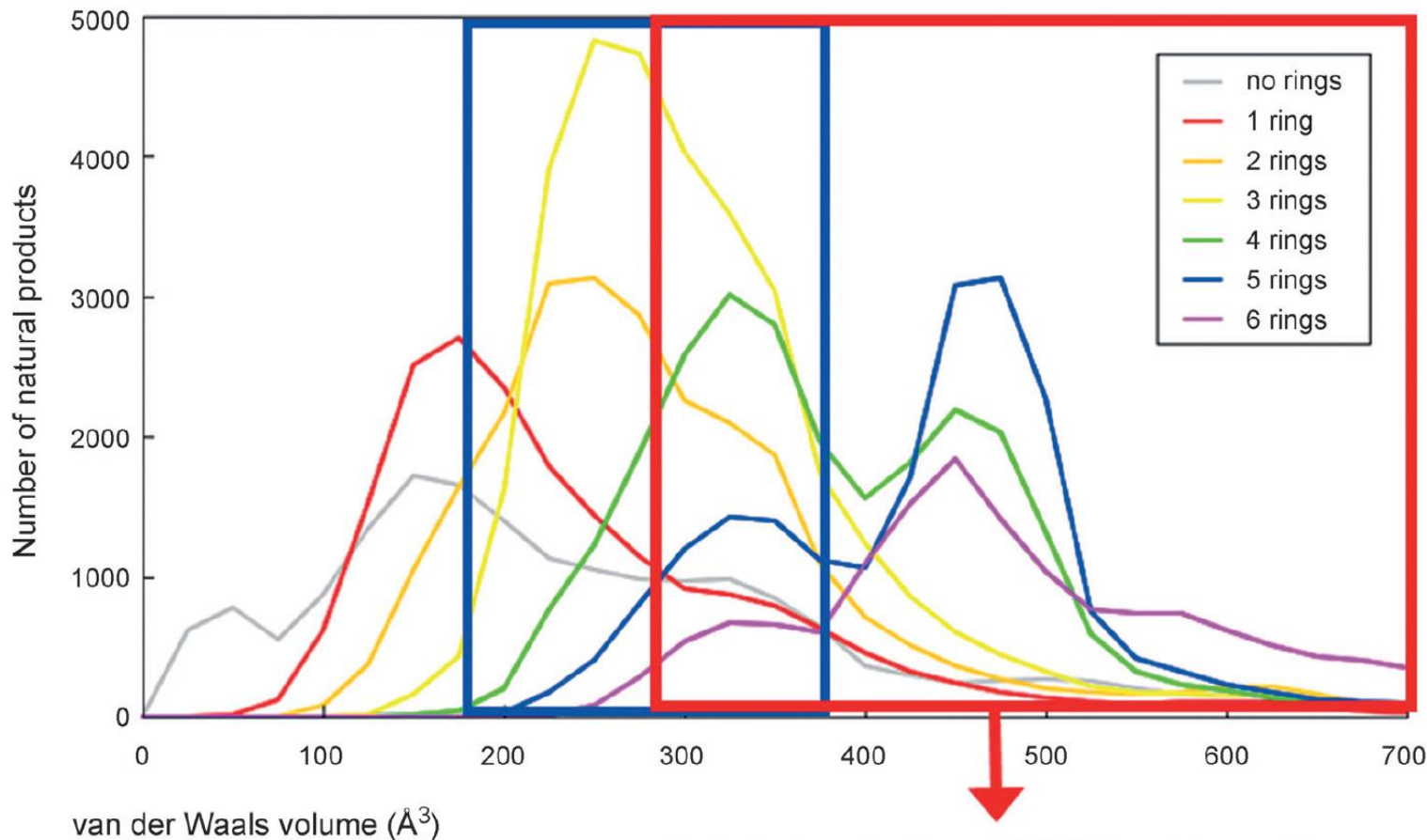
Angew. Chem. Int. Ed. 2011, 50, 10800–10826

PNs com massa molecular < 1000 g/mol e respectivo número de anéis em suas estruturas



Foco em construção de bibliotecas contendo de 2 a 4 anéis parece ser interessante.

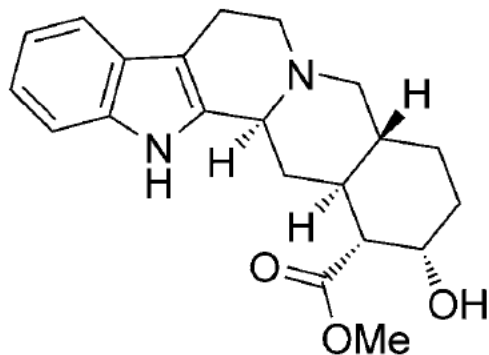
>50% dos PNs possuem scaffolds contem de 2 a 4 aneis.



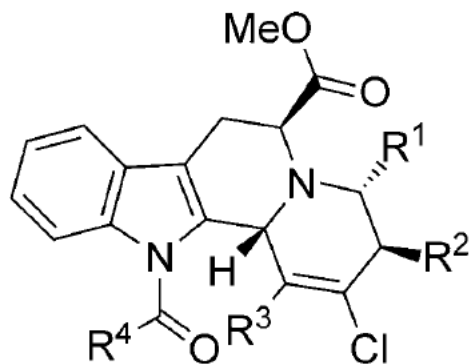
Statistical evaluation of 18 402 protein cavities:
Majority: 300–800 Å³

Tamanho certo para serem utilizados como scaffolds na diversificação

Coleções Inspiradas em PNs



Yohimbine



Scaffold relaciona-se a estrutura básica do PN.

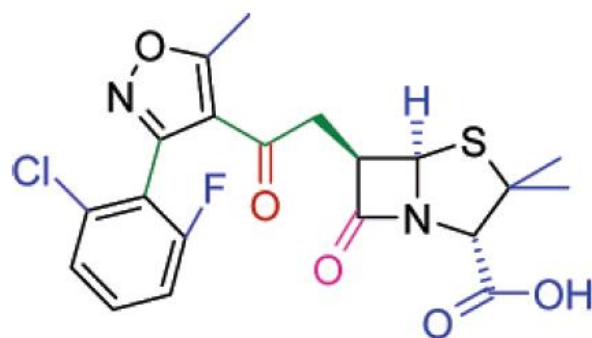
Scaffold geralmente contruído por síntese *de novo*.

Substituintes são introduzidos durante as etapas sintéticas.

Padrão de substituição pode se diferenciar do padrão presente no PN.

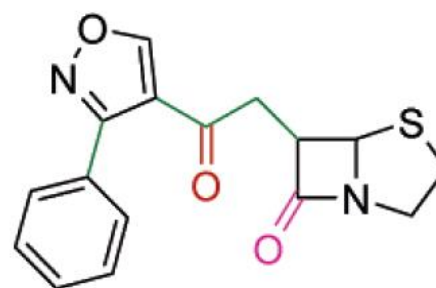
Estereoquímica pode variar.

Obtendo o Scaffold



Flucloxacillin
5290-39-5

- terminal sidechain
- linker
- exocyclic double bond
- exolinker double bond



molecular framework

Regras para obtenção de scaffolds

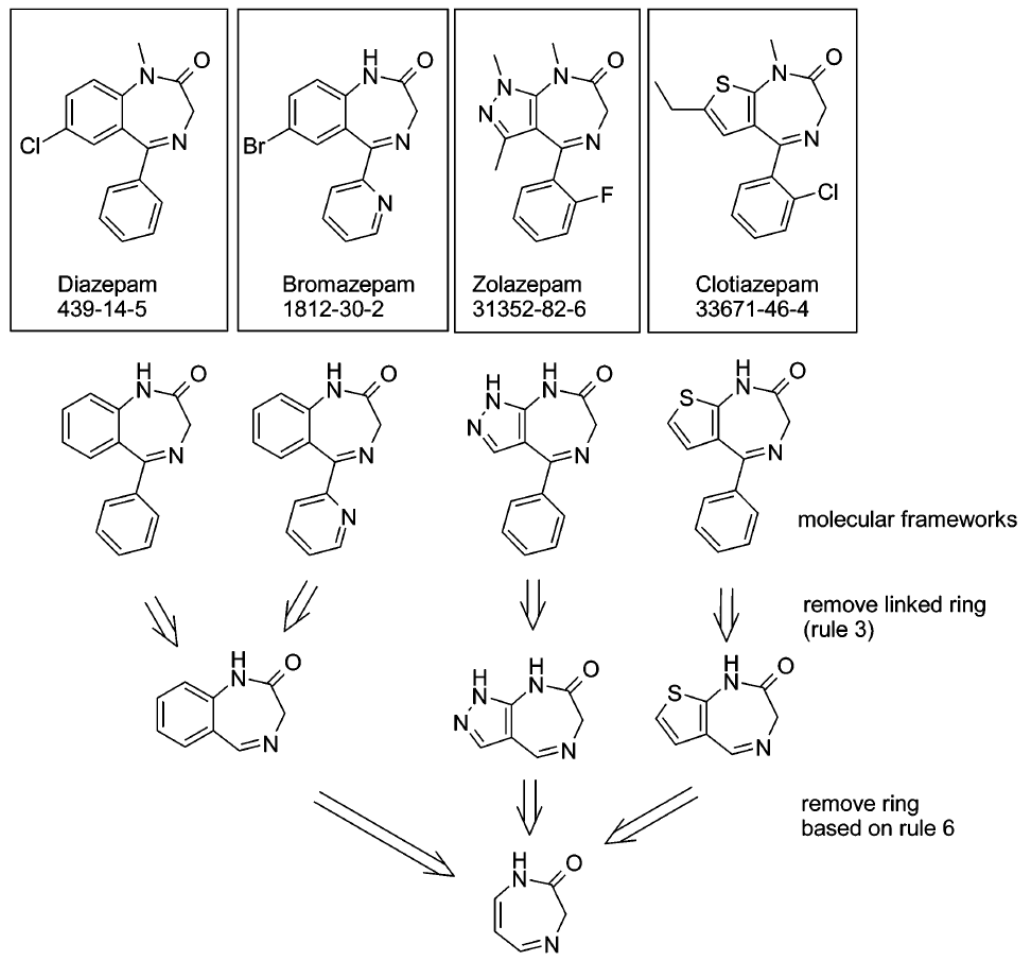
- 1. Remover Heterociclos de 3 membros.
- 2. Não remover aneis acima de 12 átomos se ainda existirem aneis menores para serem removidos.
- 3. Escolher o scaffold pai que possua o menor número de ligantes acíclicos.
- 4. Preferencialmente manter aneis em ponte, espiro e padrões não lineares de aneis.
- 5. Aneis em ponte são mantidos preferencialmente em relação a espiro.
- 6. Remover anéis de 3, 5 e 6 membros.
- 7. Um sistema aromático não pode ser quebrado de uma forma que resulte em um sistema não aromático.
- 8. Remover primeiro aneis com o menor número de heteroátomos.

Regras para obtenção de scaffolds

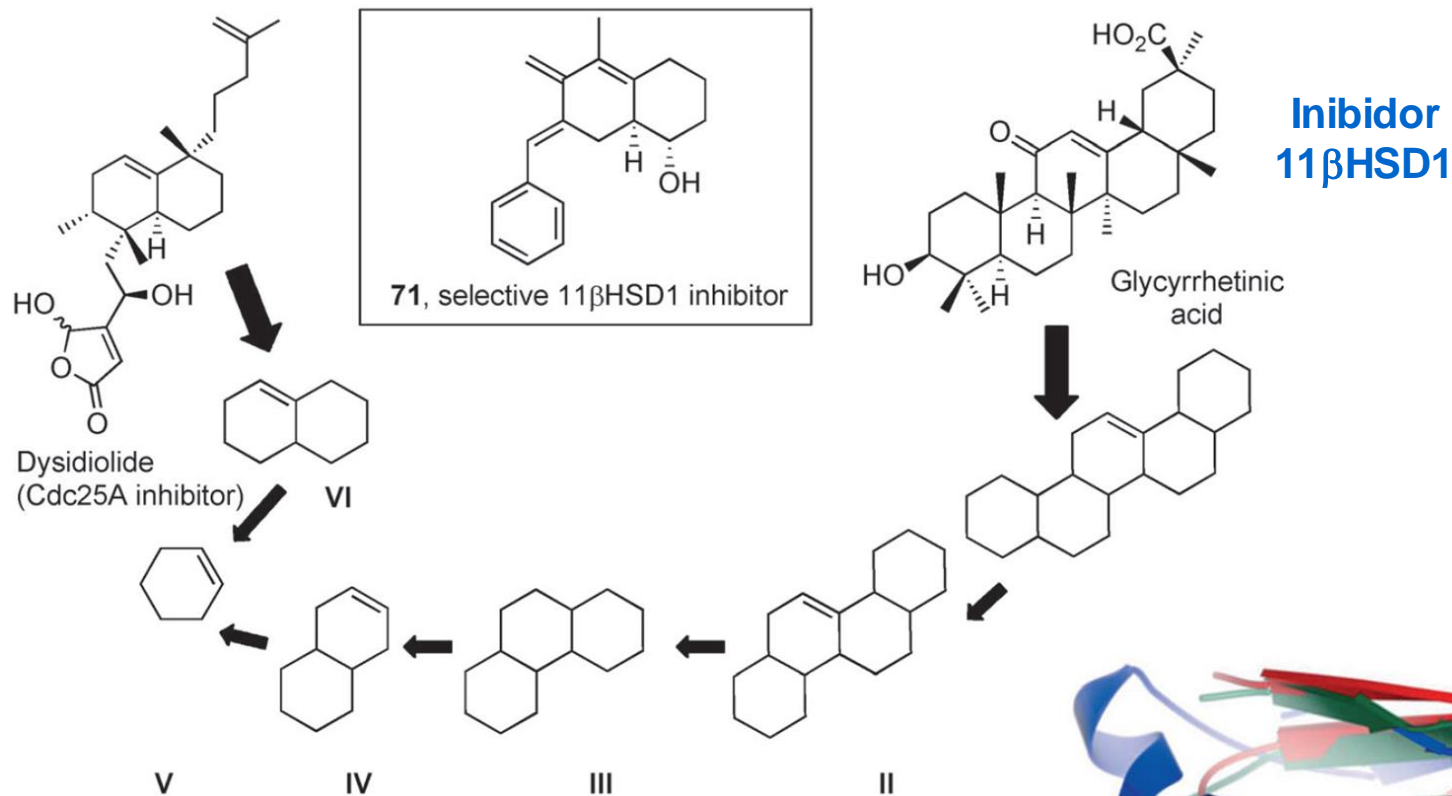
- 9. Se o número de heteroátomos é igual, a prioridade é manter anéis com heteroátomos na seguinte ordem: $N > O > S$.
- 10. Menor anel é removido.
- 11. Em sistemas mistos Aromático/não aromático, manter anéis não aromáticos como prioridade.
- 12. Remover primeiro o anel que esteja ligado a um “linker” que por sua vez esteja ligado a um anel heteroaromático em ambos os lados do “linker”.
Tiebreaking Rule.

Síntese Biologicamente Orientada (BIOS)

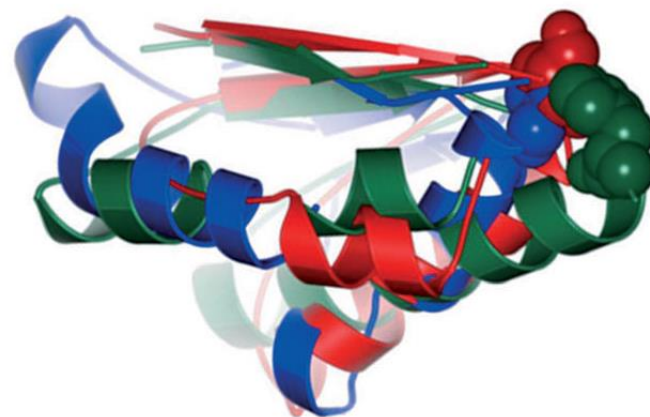
Perceba que todos os produtos são derivados de um mesmo scaffold através da deconvolução



Exemplo BIOS

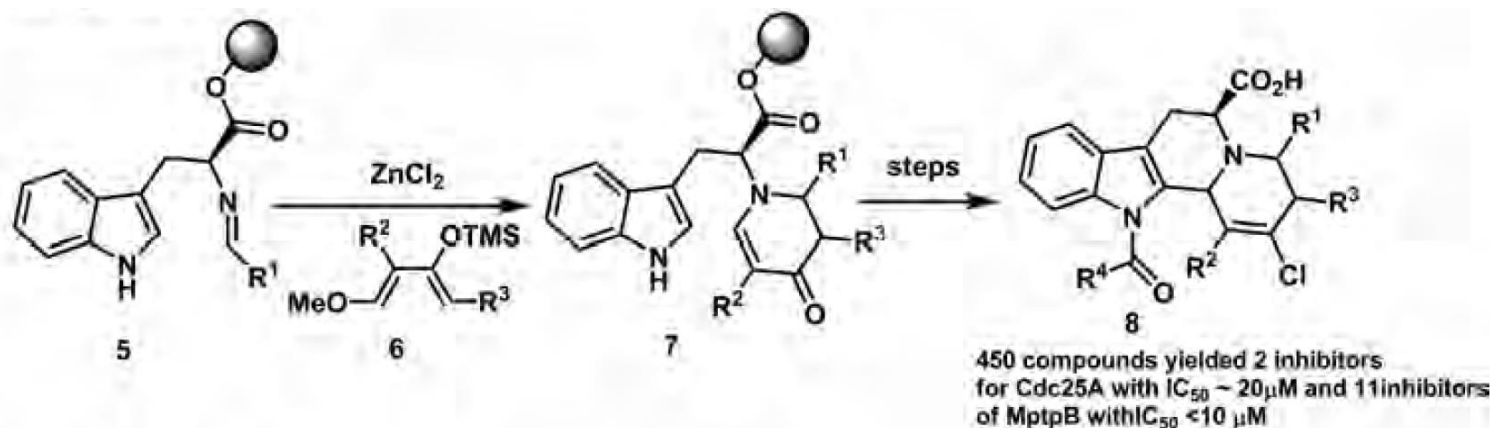
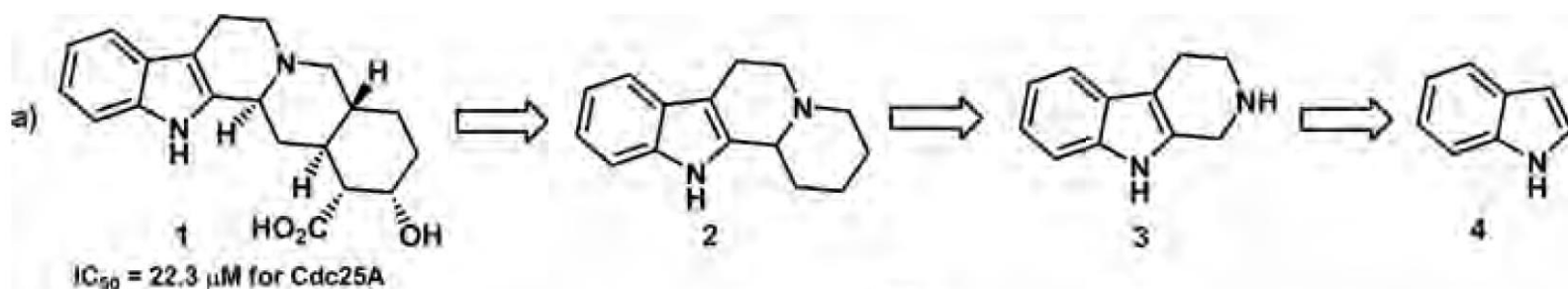


Biblioteca 483 decalinas baseadas em VI (scaffold alternativo de GA) gerou 71.



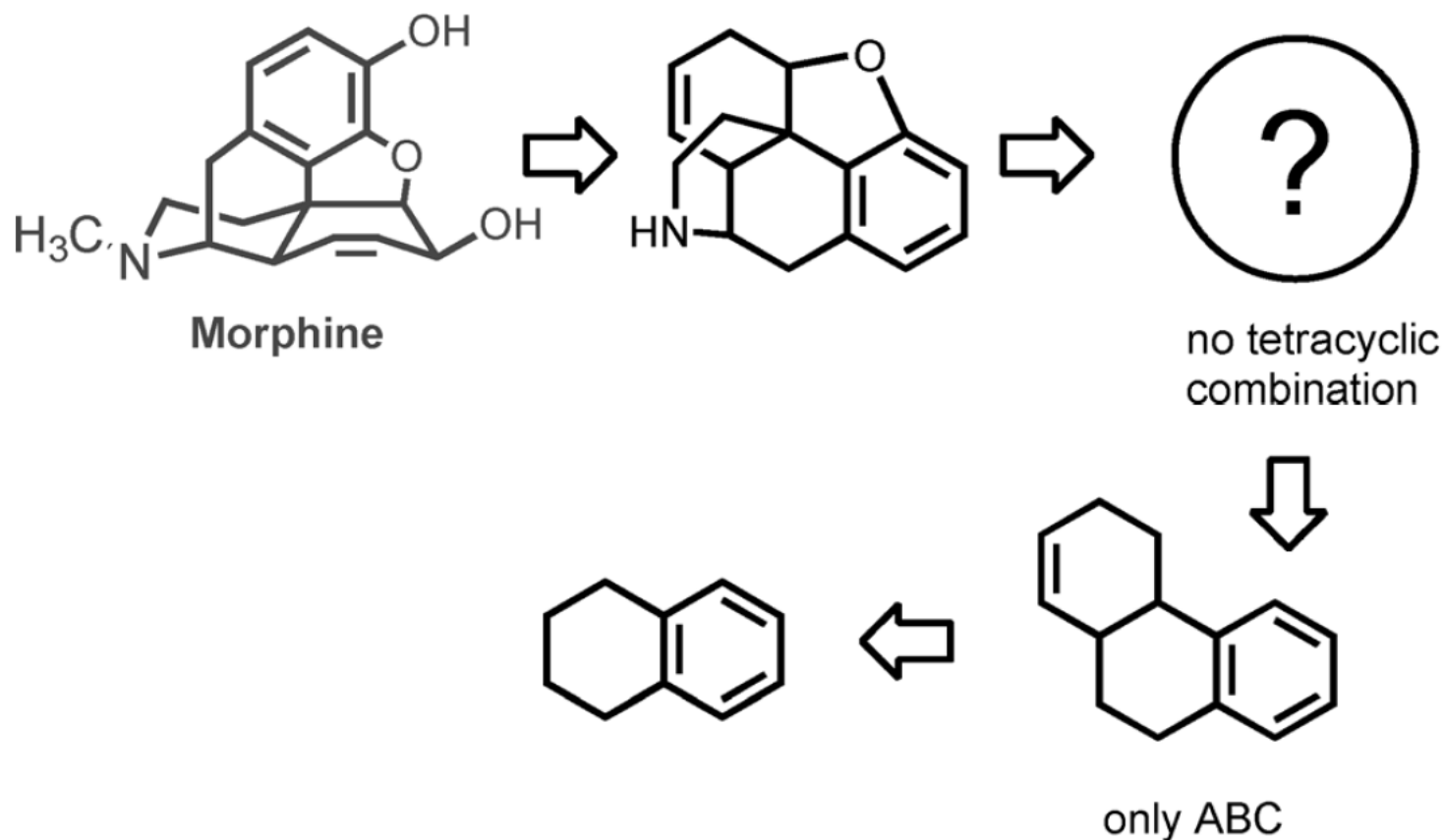
Exemplo BIOS

A yohimbine e ajmalicine (alcaloides complexos) identificados como inibidores de fosfatase Cdc25A. Simplificação estrutural dayohimbine (1) utilizando-se BIOS
 Levou a identificação de scaffolds com 4, 3, 2(indol) aneis.

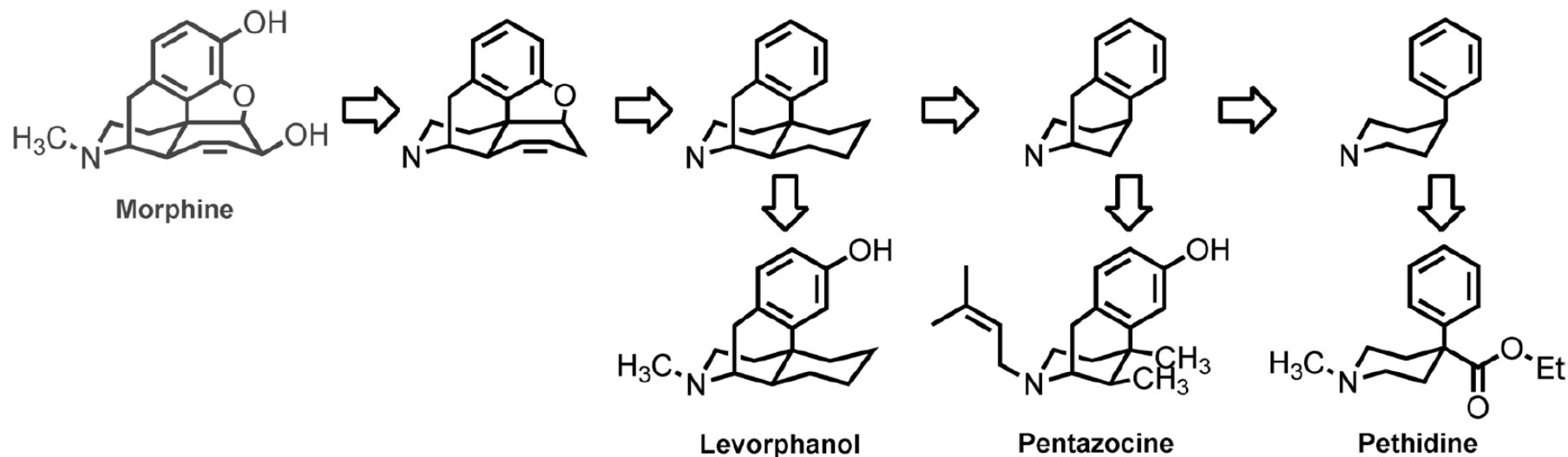


Morfina

Classificação baseada em SCONP revela furos na deconvolução de PNs.
Nenhum PN tetracíclico derivado da morfina é conhecido e apenas 1 derivado tricíclico foi encontrado na natureza.

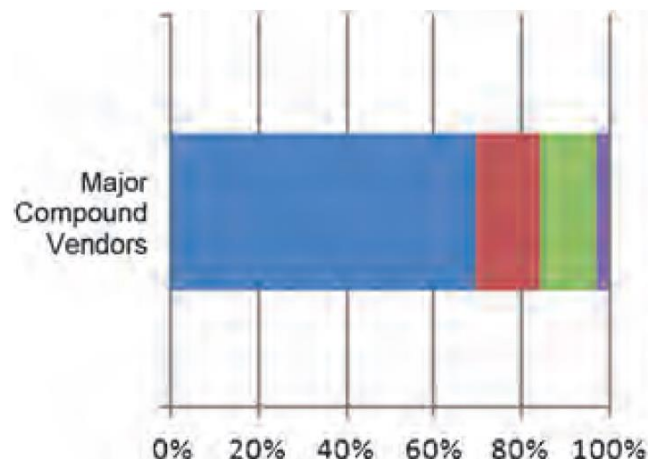
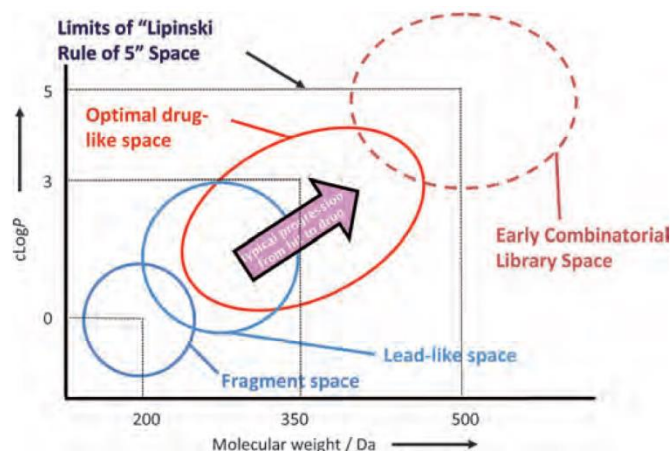


Derivados Sintéticos - Morfina



Derivados tetracíclicos da morfina transformaram-se em drogas comerciais!

Lead Oriented Synthesis (LOS)



Lead-likeness guide	Preferred Values
Lipophilicity guide	$-1 \leq cLogP \leq 3$
Molecular size guide	$14 \leq \text{heavy atoms} \leq 26$ (mw=200-350 Da)
Undesired sub-structure filters	<ul style="list-style-type: none"> Remove molecules containing chemically reactive, electrophilic or redox active groups. Favor molecules with lower degree of aromatic character and/or more 3D shape.

Fail B: grupos indesejados presentes na molécula.

The overall number of newly approved “new chemical entities” has decreased in the past 10 years and does not reflect the increase in compound collection size, research effort or financial investments.

Como procurar por produtos naturais que sejam interessantes de serem utilizados como Scaffold?

Bases de dados da Industria!!!!



The screenshot displays the PubChem website interface within a web browser. The browser's address bar shows the URL `pubchem.ncbi.nlm.nih.gov`. The website header includes navigation menus for **Databases**, **Upload**, **Services**, **Help**, and **more**. The central focus is the **PubChem** logo and a search bar with a **GO** button and a link to **Advanced Search**. Below the search bar, there are links for **Structure Search**, **BioActivity Analysis**, and **BioActivity DataDicer**. A sidebar on the right side of the page lists various tools and services, including **BioActivity Summary**, **BioActivity Datable**, **BioActivity SAR**, **BioActivity DataDicer**, **Structure Search**, **3D Conformer Tools**, **Structure Clustering**, **Classification**, **Upload**, **Download**, and **PubChem FTP**. At the bottom of the page, there is a footer with links for **Write to Helpdesk**, **Disclaimer**, **Privacy Statement**, **Accessibility**, and **Data Citation Guidelines**, along with the text **National Center for Biotechnology Information, NLM | NIH | HHS**. The Windows taskbar at the bottom shows the Start button, several application icons, and the system tray with the date **14/11/2013** and time **15:37**.

EMBL-EBI

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Please enter a list of Compound IDs, keywords, or SMILES separated by newlines

Fetch Compounds

Biologicals Blast Search

Run BLAST

Substructure Search 100% Fetch Compounds

ChEMBL Statistics

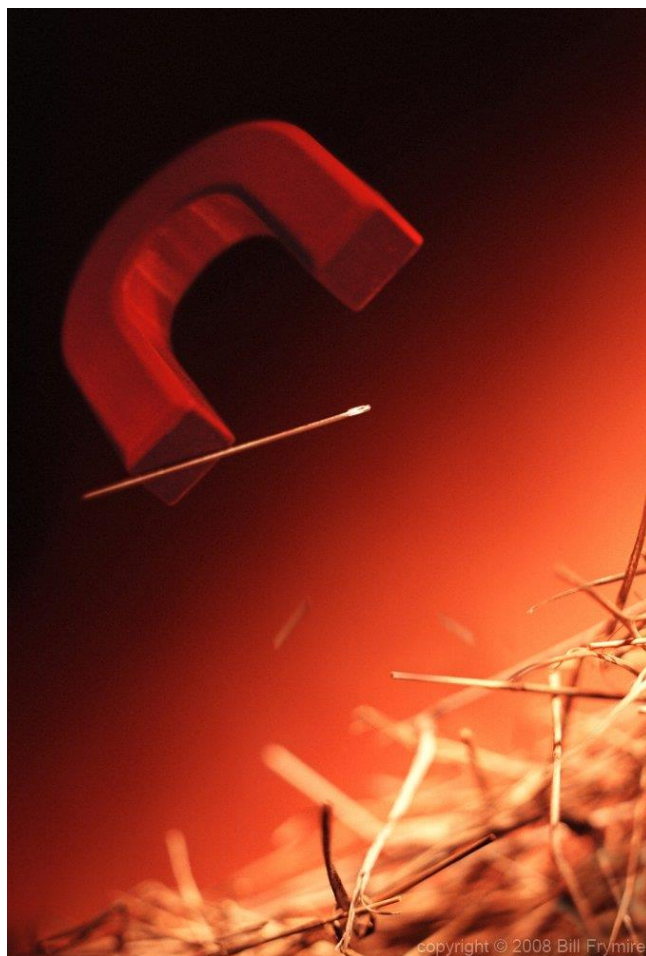
- DB: ChEMBL_17
- Targets: 9,356
- Compound records: 1,520,172
- Distinct compounds: 1,324,941
- Activities: 12,077,491
- Publications: 51,277
- [Release Notes](#)

ChEMBL Blog

- [New ChEMBL-NTD Depositions](#)
- [RDKit and Rachael.js](#)

JSME Molecular Editor by Peter Ertl and Bruno Bienfait

15:40 14/11/2013



Conclusão

Journal of
**Medicinal
Chemistry**

Perspective

pubs.acs.org/jmc

Lessons from Natural Products Chemistry Can Offer Novel Approaches for Synthetic Chemistry in Drug Discovery

Miniperspective

Natalya I. Vasilevich,* Roman V. Kombarov, Dmitry V. Genis, and Michael A. Kirpichenok

J. Med. Chem. 2012, 55, 7003–7009

Inspirar-se em Produtos Naturais é uma Grande oportunidade para Químicos Sintéticos!!!