Tópicos Especiais em Química Medicinal

Aula 2 – 27/05

Tópicos Especiais
em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos


UFRJ
ICARIAN
ICARIAN
ICARIAN

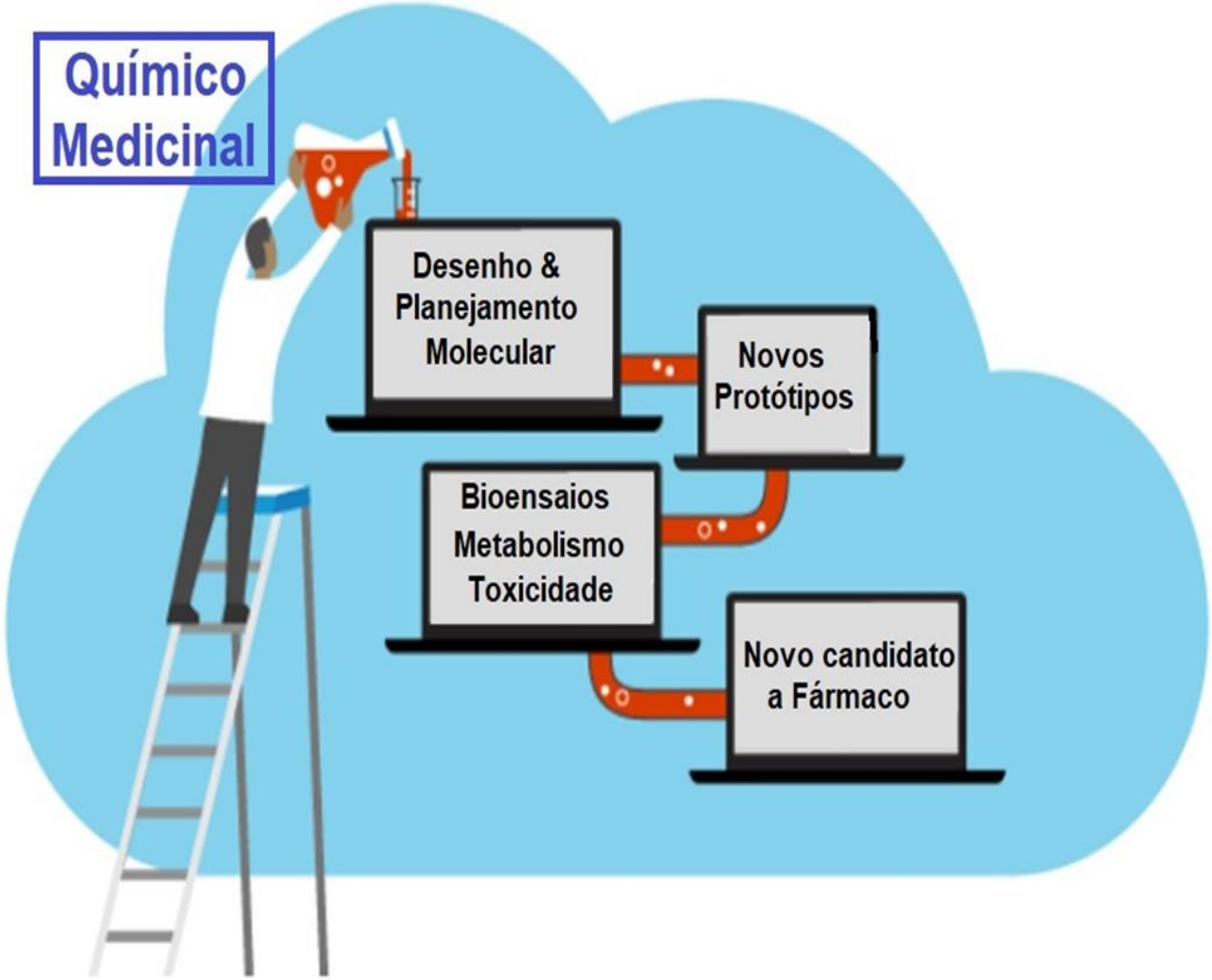
Exercício #1

Definição de

Química Medicinal

Faça uma definição comentada de QM, EM ATÉ 30 LINHAS, com suas palavras e referência(s).

Química Medicinal



Adaptada de

IUPAC

Pure & Appl. Chem., Vol. 70, No. 5, pp. 1129–1143, 1998.
Printed in Great Britain.

Química
med
Medicinal
chem

Etapa de Pesquisa

Lead compound
Composto-protótipo

Inicial: Realização dos ensaios pré-clínicos
Tardia: Realização dos ensaios clínicos (Fase I, Fase II e Fase III [Fase IV]).

Etapa de Desenvolvimento

Seleção do alvo molecular; Desenho molecular de ligantes; Síntese – série congênere; Identificação & Otimização do Composto-Protótipo; Ensaios farmacológicos *in vitro* & *in vivo*;

Marketing & vendas

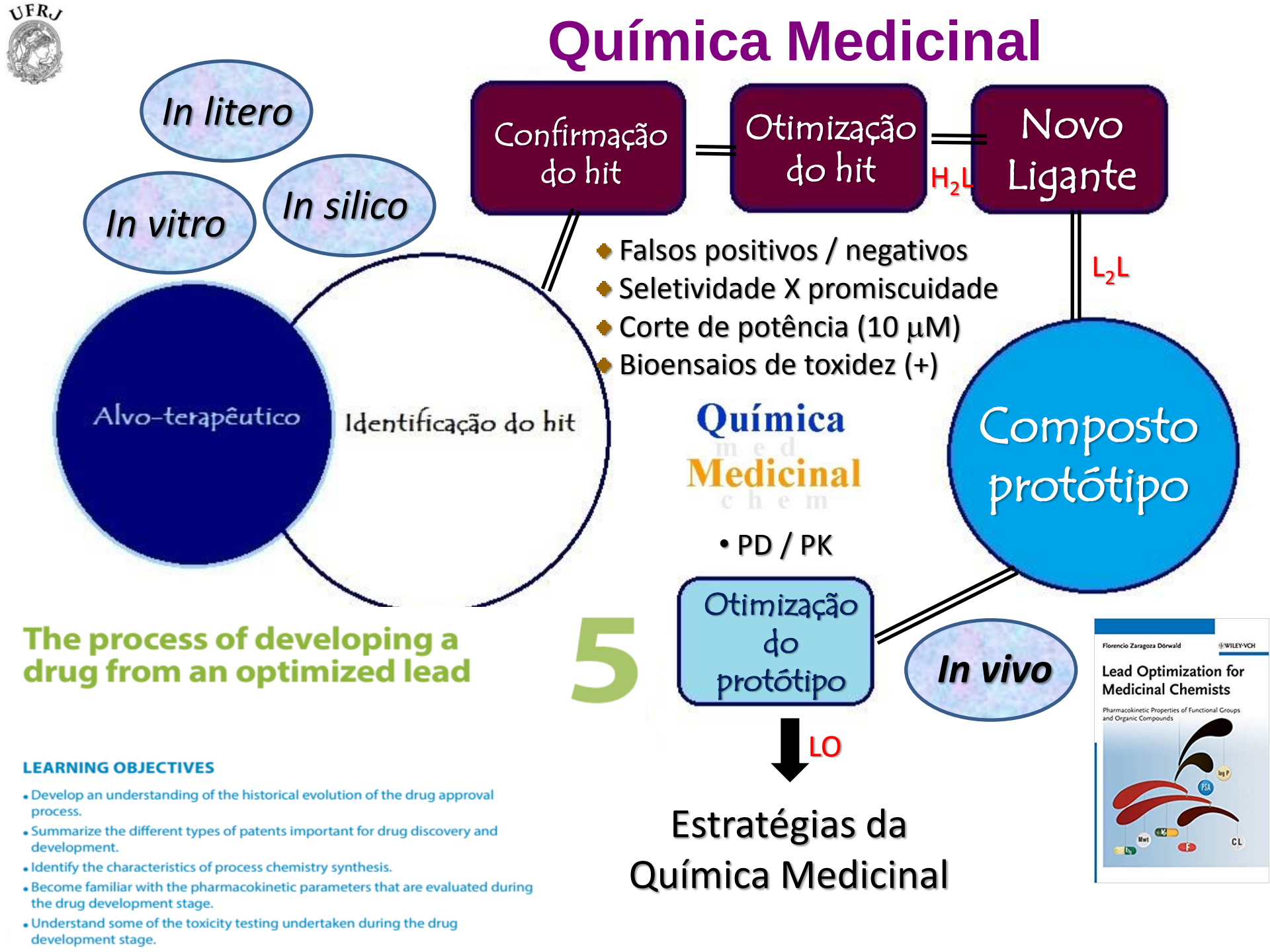
Farmaco-vigilância

Etapa de Comercialização

Etapa Regulatória

ANVISA

Química Medicinal



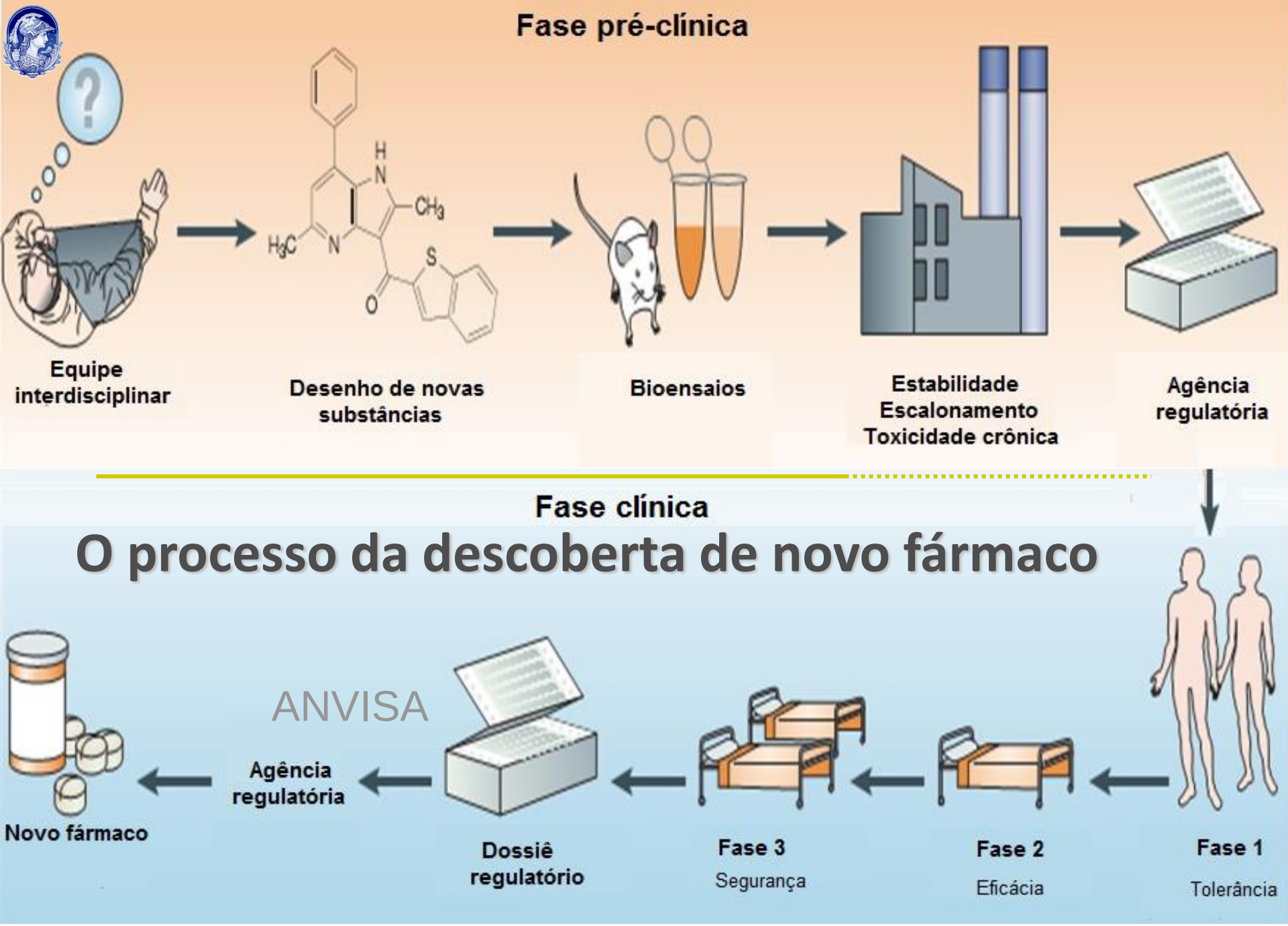
The process of developing a drug from an optimized lead

5

LEARNING OBJECTIVES

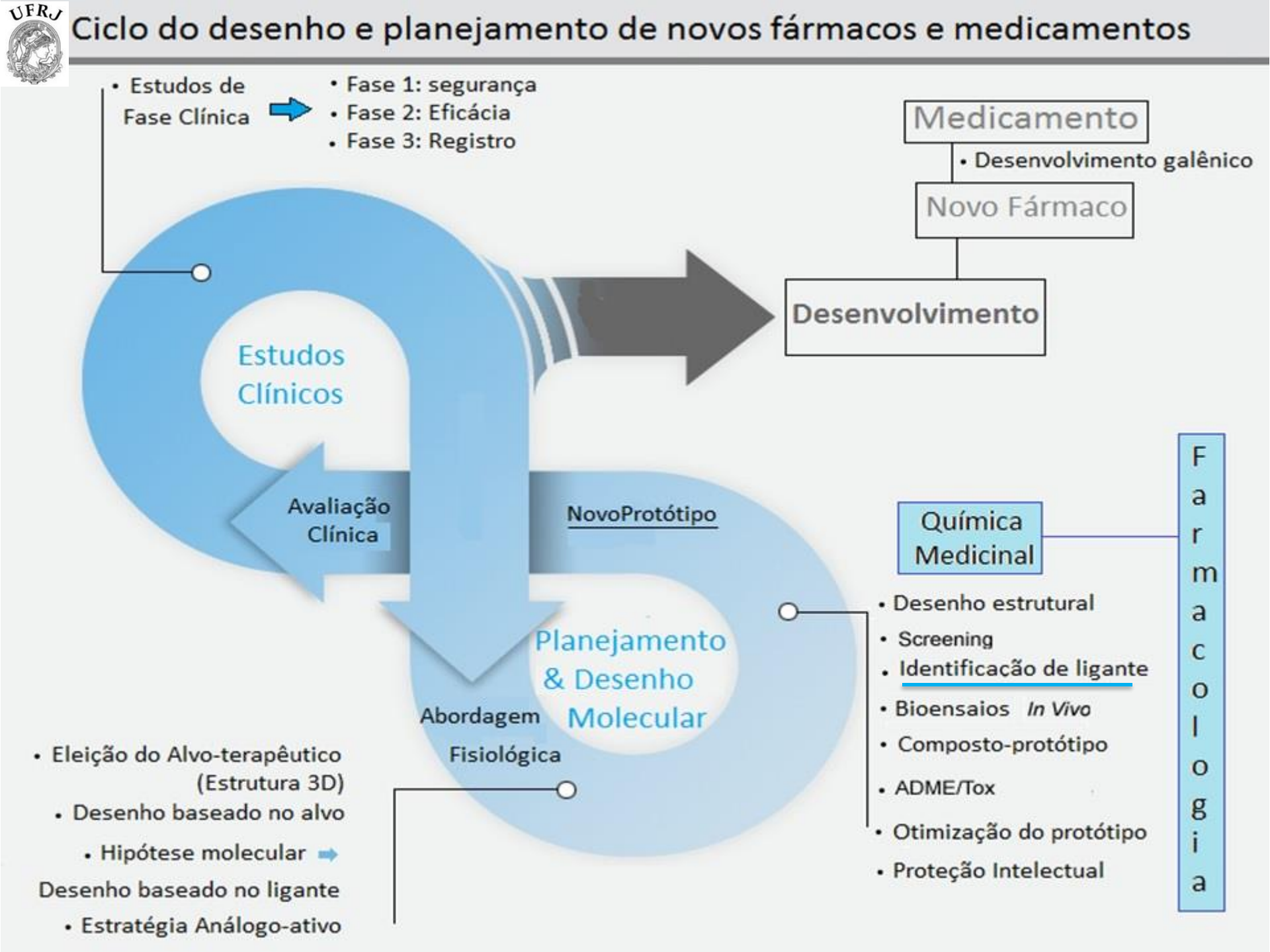
- Develop an understanding of the historical evolution of the drug approval process.
- Summarize the different types of patents important for drug discovery and development.
- Identify the characteristics of process chemistry synthesis.
- Become familiar with the pharmacokinetic parameters that are evaluated during the drug development stage.
- Understand some of the toxicity testing undertaken during the drug development stage.

O processo da descoberta de novo fármaco

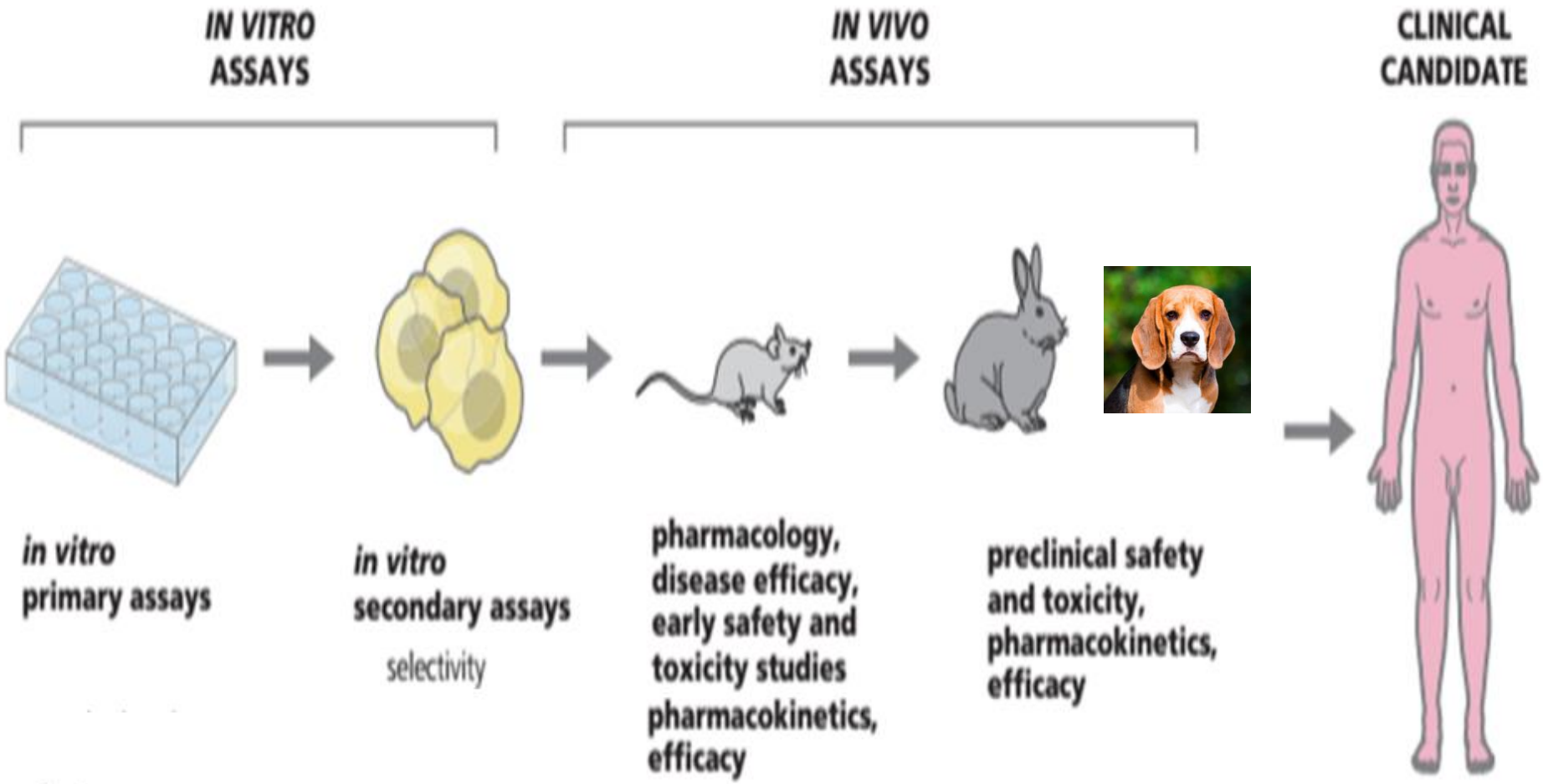


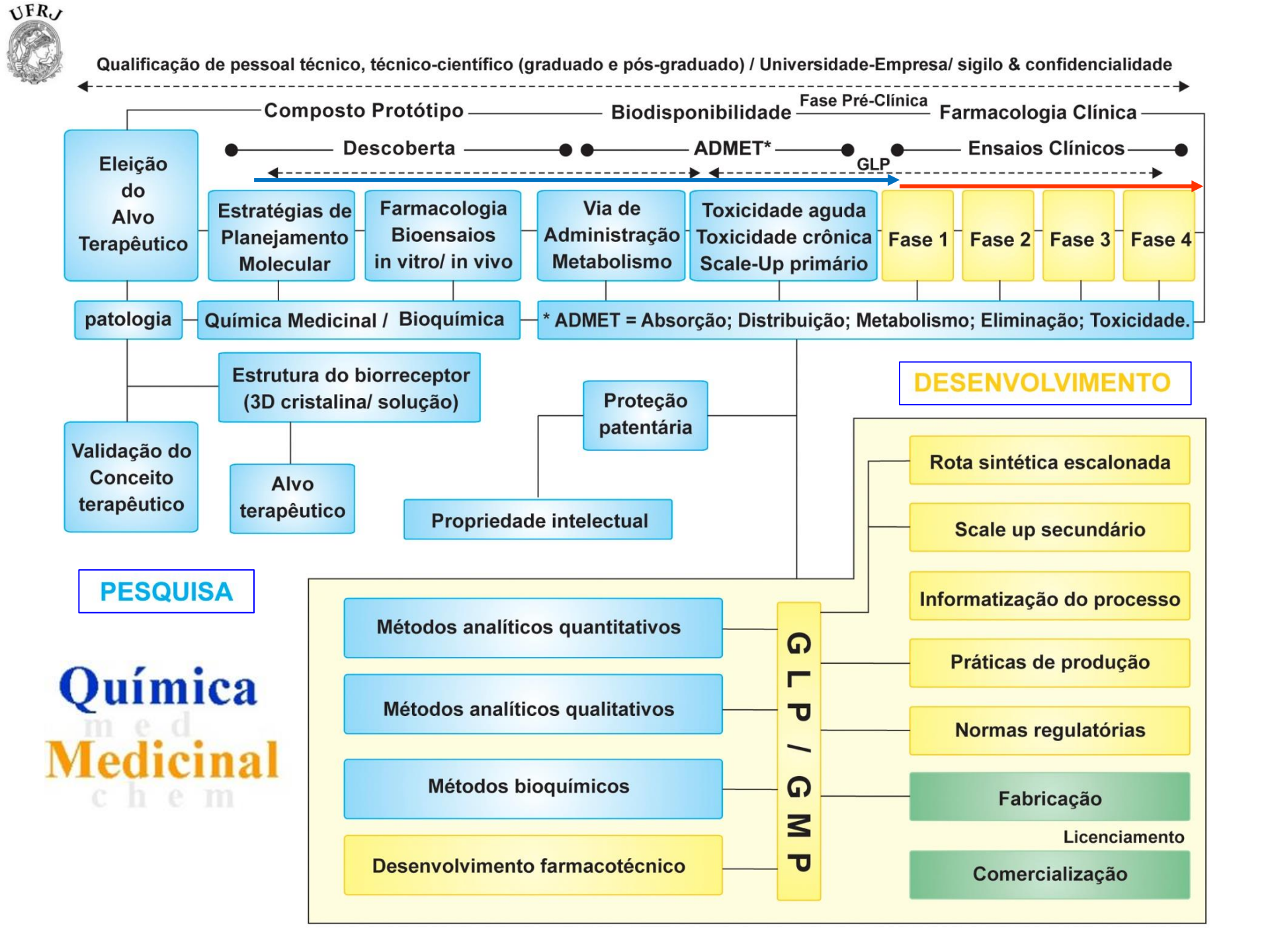
Adaptado de JA Lombardino & JA Lowe III, *Nat Rev Drug Discov* **2004**, *3*, 853.

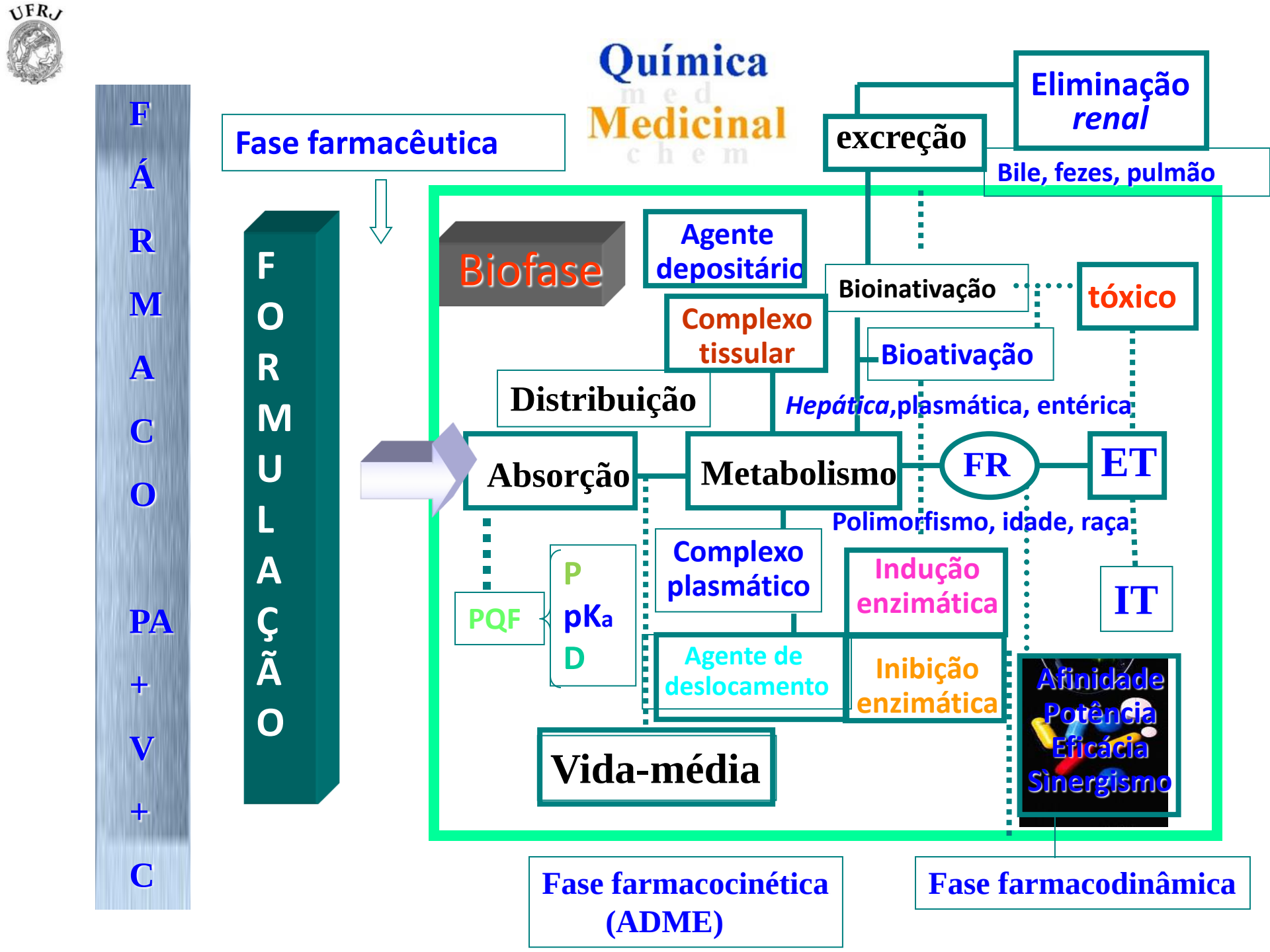
Ciclo do desenho e planejamento de novos fármacos e medicamentos



Otimização das propriedades PD (interações F-R) & PK (drug-like properties)




Qualificação de pessoal técnico, técnico-científico (graduado e pós-graduado) / Universidade-Empresa/ sigilo & confidencialidade
Composto Protótipo
Biodisponibilidade
Fase Pré-Clínica
Farmacologia Clínica
Descoberta
ADMET*
Ensaios Clínicos
GLP
Eleição do Alvo Terapêutico
Estratégias de Planejamento Molecular
Farmacologia Bioensaios in vitro/ in vivo
Via de Administração Metabolismo
Toxicidade aguda Toxicidade crônica Scale-Up primário
Fase 1
Fase 2
Fase 3
Fase 4
patologia
Química Medicinal / Bioquímica
* ADMET = Absorção; Distribuição; Metabolismo; Eliminação; Toxicidade.
Estrutura do biorreceptor (3D cristalina/ solução)
Proteção patentária
DESENVOLVIMENTO
Validação do Conceito terapêutico
Alvo terapêutico
Propriedade intelectual
PESQUISA
Rota sintética escalonada
Scale up secundário
Informatização do processo
Práticas de produção
Normas regulatórias
Fabricação
Licenciamento
Comercialização
Métodos analíticos quantitativos
Métodos analíticos qualitativos
Métodos bioquímicos
Desenvolvimento farmacotécnico
G L P / G M P
Química
med
Medicinal
chem


Química
med
Medicinal
chem
FÁRMACO PA + V + C
Fase farmacêutica
FORMULAÇÃO
Biofase
Agente depositário
Complexo tissular
Distribuição
Absorção
Metabolismo
PQF
P
pKa
D
Complexo plasmático
Agente de deslocamento
Vida-média
excreção
Eliminação renal
Bile, fezes, pulmão
Bioinativação
tóxico
Bioativação
Hepática,plasmática, entérica
FR
ET
Polimorfismo, idade, raça
Indução enzimática
Inibição enzimática
IT
Afinidade
Potência
Eficácia
Sinergismo
Fase farmacocinética (ADME)
Fase farmacodinâmica

Metabolismo de fármacos

2

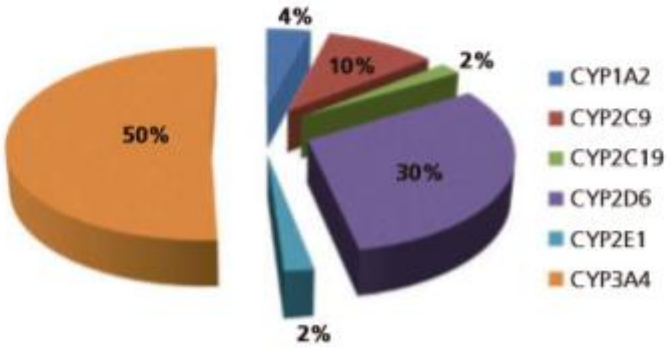
FUNDAMENTOS DO METABOLISMO DE FÁRMACOS

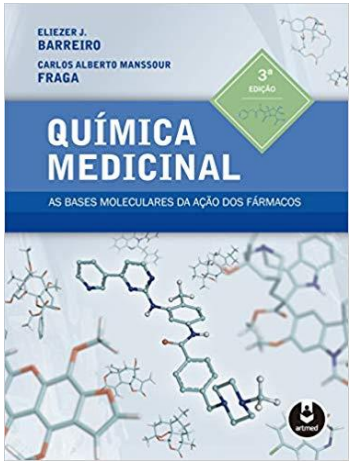
LÍDIA MOREIRA LIMA

ASPECTOS GERAIS DO METABOLISMO DE FÁRMACOS

O metabolismo compreende o parâmetro farmacocinético diretamente ligado à depuração (do inglês *clearance*) dos fármacos, contribuindo para evitar seu acúmulo indesejado na biofase. O papel fisiológico do metabolismo de fármacos pode ser medido por meio dos parâmetros farmacocinéticos de biodisponibilidade (F) e *clearance* (Cl).

Contribuição ao metabolismo oxidativo de fármacos

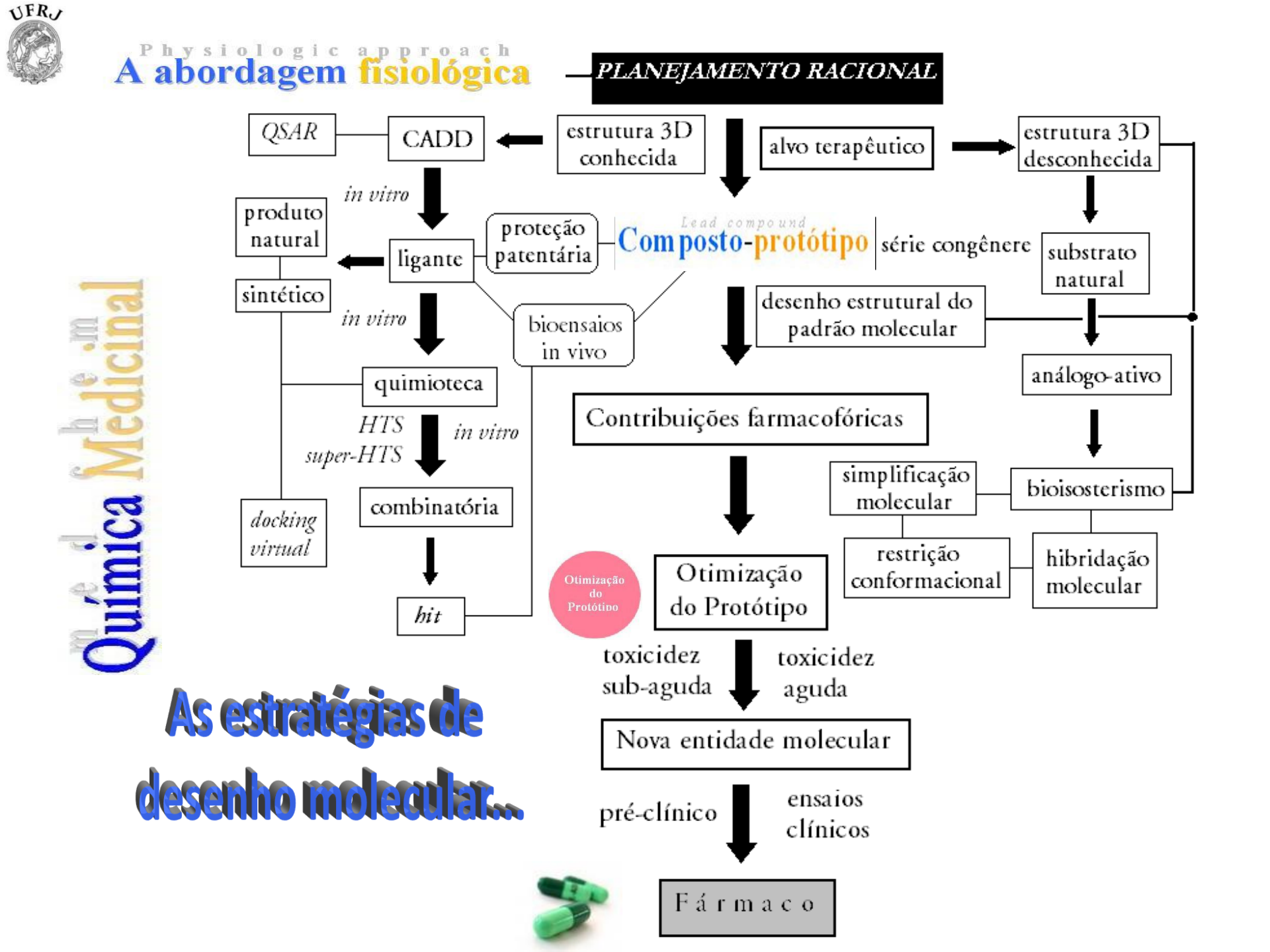




pp. 43-103

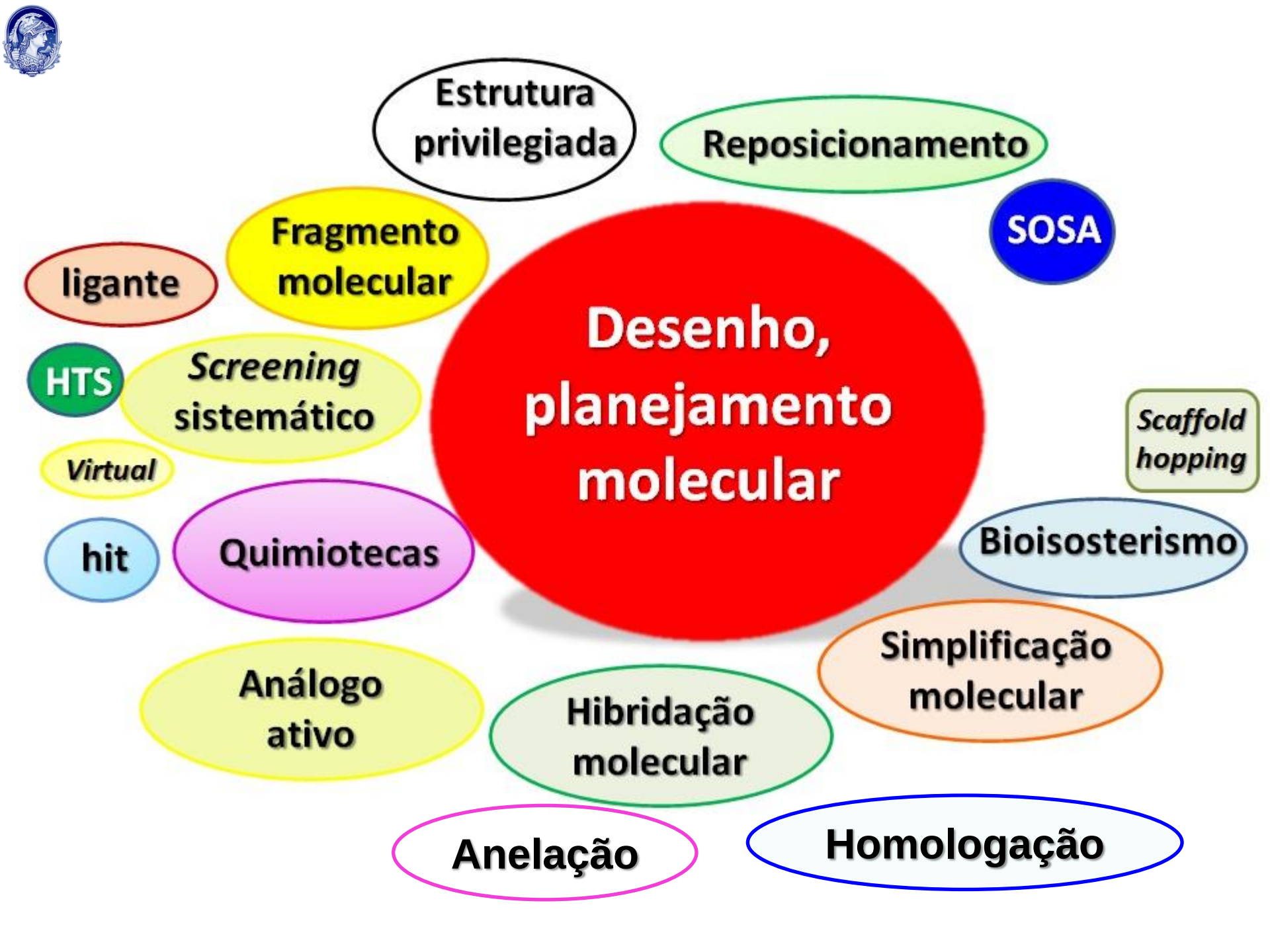
Physiologic approach

A abordagem fisiológica



Química Medicinal

As estratégias de desenho molecular...


Desenho, planejamento molecular
Estrutura privilegiada
Reposicionamento
SOSA
Fragmento molecular
ligante
HTS
Screening sistemático
Virtual
Scaffold hopping
Bioisosterismo
hit
Quimiotecas
Simplificação molecular
Análogo ativo
Hibridação molecular
Anelação
Homologação

Current Topics in Medicinal Chemistry, 2019, *19*, 1679-1693

REVIEW ARTICLE

BENTHAM SCIENCE

Chemical Intuition in Drug Design and Discovery

Abstract: The medicinal chemist plays the most important role in drug design, discovery and development. The primary goal is to discover leads and optimize them to develop clinically useful drug candidates. This process requires the medicinal chemist to deal with large sets of data containing chemical descriptors, pharmacological data, pharmacokinetics parameters, and *in silico* predictions. The modern medicinal chemist has a large number of tools and technologies to aid him in creating strategies and supporting decision-making. Alongside with these tools, human cognition, experience and creativity are fundamental to drug research and are important for the chemical intuition of medicinal chemists. Therefore, fine-tuning of data processing and in-house experience are essential to reach clinical trials. In this article, we will provide an expert opinion on how chemical intuition contributes to the discovery of drugs, discuss where it is involved in the modern drug discovery process, and demonstrate how multidisciplinary teams can create the optimal environment for drug design, discovery, and development.

Keywords: Chemical Intuition, Medicinal Chemistry, Drug Discovery, Lead Optimization, Structure-Activity Relationship, Decision-making, History of Drug Discovery.

PLOS ONE **2012**, *7* (11), e48476

OPEN ACCESS Freely available online . doi:10.1371/journal.pone.0048476

PLOS ONE

Inside the Mind of a Medicinal Chemist: The Role of Human Bias in Compound Prioritization during Drug Discovery

Peter S. Kutchukian[1], Nadya Y. Vasilyeva[2], Jordan Xu[3], Mika K. Lindvall[3], Michael P. Dillon[3], Meir Glick[1], John D. Coley[2]*, Natasja Brooijmans[4]*

1 Center for Proteomic Chemistry, Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, United States of America, **2** Department of Psychology, Northeastern University, Boston, Massachusetts, United States of America, **3** Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Emeryville, California, United States of America, **4** Blueprint Medicines, Cambridge, Massachusetts, United States of America

- "Medicinal chemists' "intuition" is critical for success in modern drug discovery…"

Drug Discovery Today • Volume 00, Number 00 • December 2019 REVIEWS

ELSEVIER

The next level in chemical space navigation: going far beyond enumerable compound libraries

Reviews • INFORMATICS

Torsten Hoffmann[1] and Marcus Gastreich[2]

[1] Taros Chemicals GmbH & Co. KG, Emil-Figge-Str. 76a, 44227 Dortmund, Germany
[2] BioSolveIT GmbH, An der Ziegelei 79, 53757 Sankt Augustin, Germany

Recent innovations have brought pharmacophore-driven methods for navigating virtual chemical spaces, the size of which can reach into the billions of molecules, to the fingertips of every chemist. There has been a paradigm shift in the underlying computational chemistry that drives chemical space search applications, incorporating intelligent reaction knowledge into their core so that they can readily deliver commercially available molecules as nearest neighbor hits from within giant virtual spaces. These vast resources enable medicinal chemists to execute rapid scaffold-hopping experiments, rapid hit expansion, and structure-activity relationship (SAR) exploitation in largely intellectual property (IP)-free territory and at unparalleled low cost.

Introduction

For a long time, computational chemists have attempted to propose new ideas for lead molecules by tapping into novel IP spaces using techniques such as hit expansion, SAR exploitation, and scaffold hopping, yet the past 25 years have shown us that current computational algorithms and methods simply might not be capable of identifying highly innovative nearest neighbor molecules with much success. However, novel computational approaches now make it possible to identify new molecules that gain wide acceptance from medicinal chemists. Past experience has shown that it is decisive to incorporate synthetic knowledge into pharmacophore-based similarity searches in huge virtual chemistry spaces. This has been done using elegant computational algorithms that are extremely fast and easy to use, and that can take pharmacophore-based information into consideration. It has proved equally important to involve medicinal chemists during the generation of results *in silico*. The best currently available methods can search spaces close to the 4 billion molecule mark, and offer guaranteed delivery of successfully synthesized, tangible compounds, making rapid biological characterization from such enormous virtual chemistry spaces a realistic possibility [1].

Lead optimization projects in drug discovery often reach a dead end and result in failure. These projects not only try to exploit hitherto undiscovered modes of action, but may also examine the possibility of larger molecules as acting agents, such as peptides, macrocycles, biologics, and their conjugates. However, many research programs simply suffer from a lack of fast access to novel chemical classes that may display highly potent and selective pharmacological effects. On the one hand, access to larger molecular spaces is required to increase the likelihood of finding something 'interesting', whereas, on the other, methods for searching these spaces must be quicker, more efficient, and easy to use. Current chemical spaces range in size from a few thousand to 10^3 molecules offered by specialized suppliers offer ('small'), up to 10^8 ('large') for supplier pools, such as Molport, Chemspace, eMolecules, and others. Sizes considerably beyond 10^8 molecules ('giant') [2–4] can be considered as not practically tractable with traditional methods for various reasons that we discuss further below.

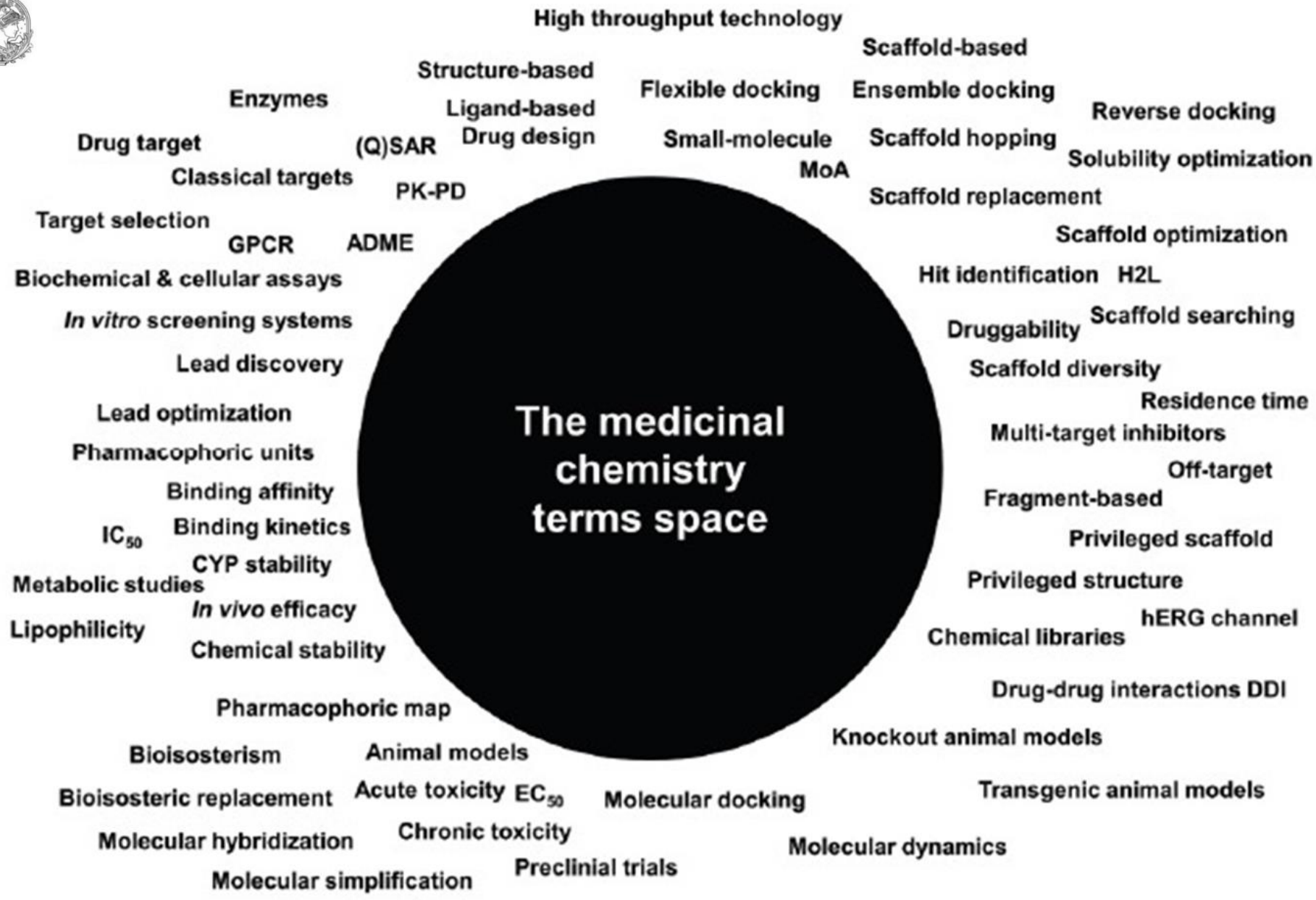
The pressure to be grand: novelty and IP

Beyond the obvious therapeutic focus, novelty is equally important. Only new IP can be patented and, thus, generate profit to finance further research in the search of new therapeutics. The solution to the search space size problem is to expand the realms of possibility using virtual molecules. One of the most prominent examples is the

Corresponding author. Gastreich, M. (gastreich@biosolveit.de)

https://doi.org/10.1016/j.drudis.2019.02.013 www.drugdiscoverytoday.com 1

Please cite this article in press as: Hoffmann, T., Gastreich, M. The next level in chemical space navigation: going far beyond enumerable compound libraries, Drug Discov Today (2019), https://doi.org/10.1016/j.drudis.2019.02.013



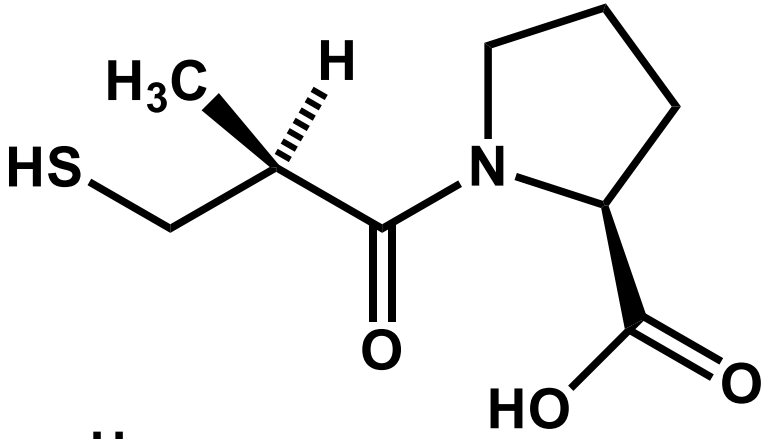
Some classical terms in medicinal chemistry (on the left side of the black circle) and some recent/modern terms in medicinal chemistry (on the right side of the black circle).

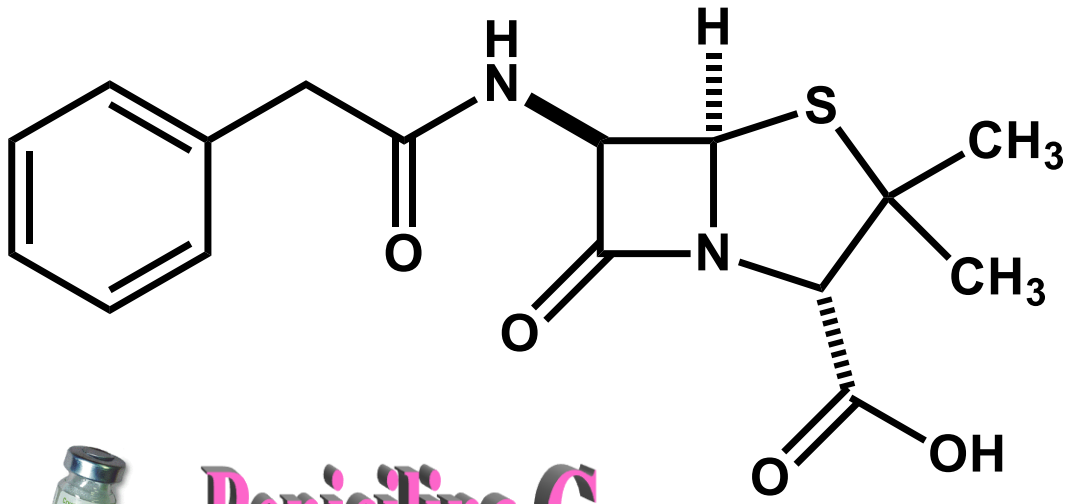
Exercício # 2

Química Medicinal

Captopril

O quê V. identifica de comum e incomum, **molecularmente**, nestes dois fármacos?



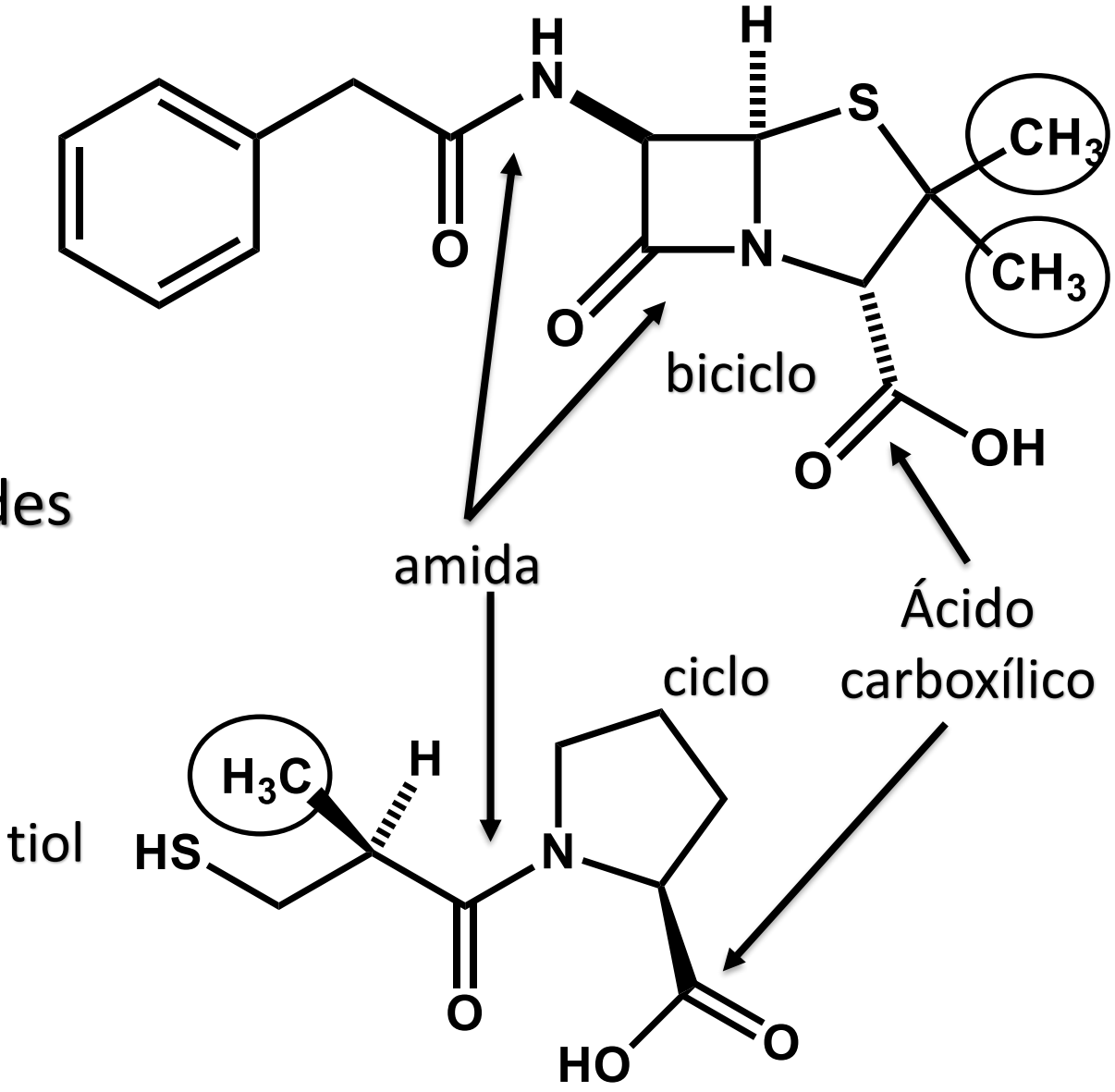


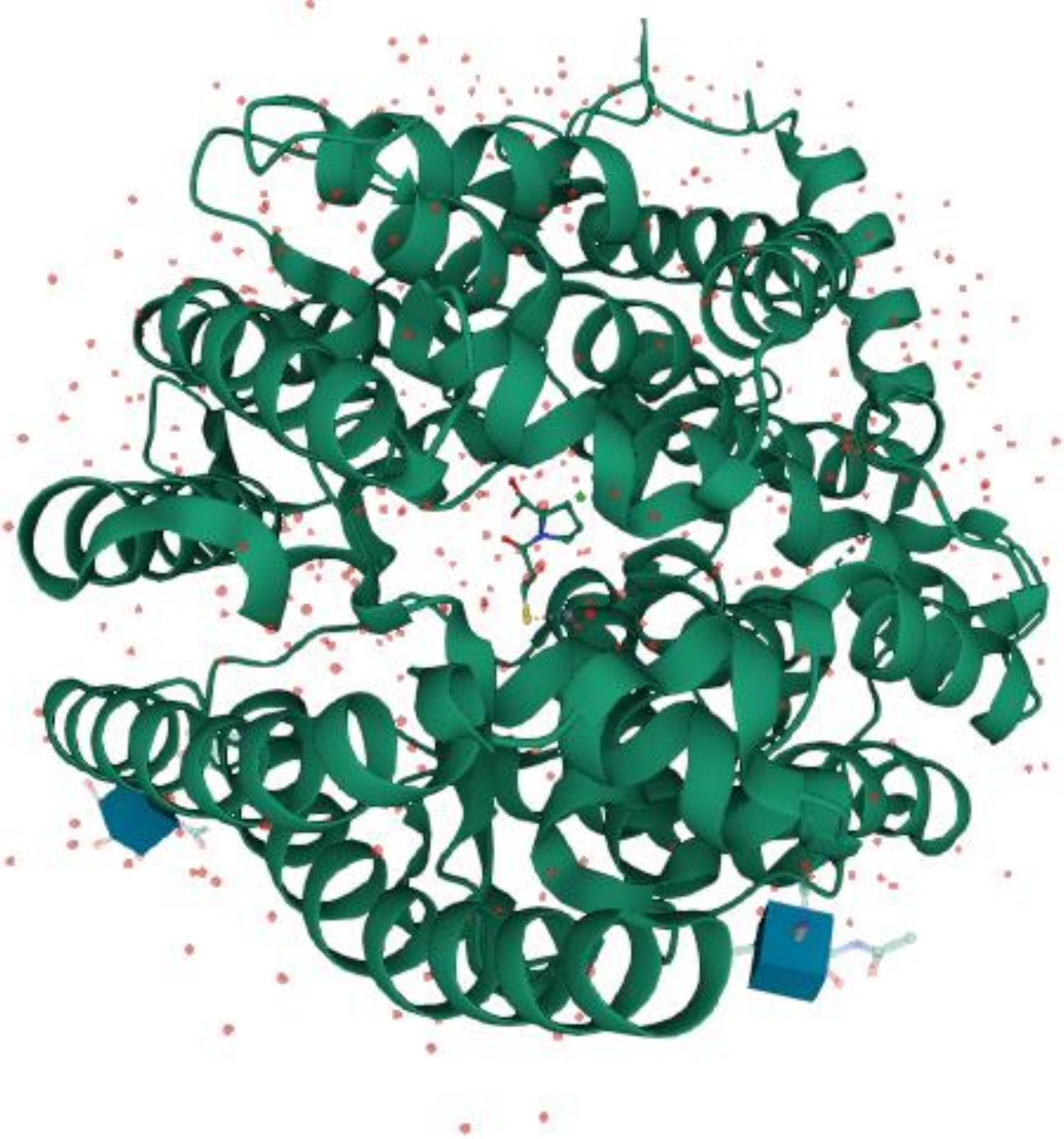
Penicilina G

Dica: Como princípio: "a linguagem da Química é a estrutura".

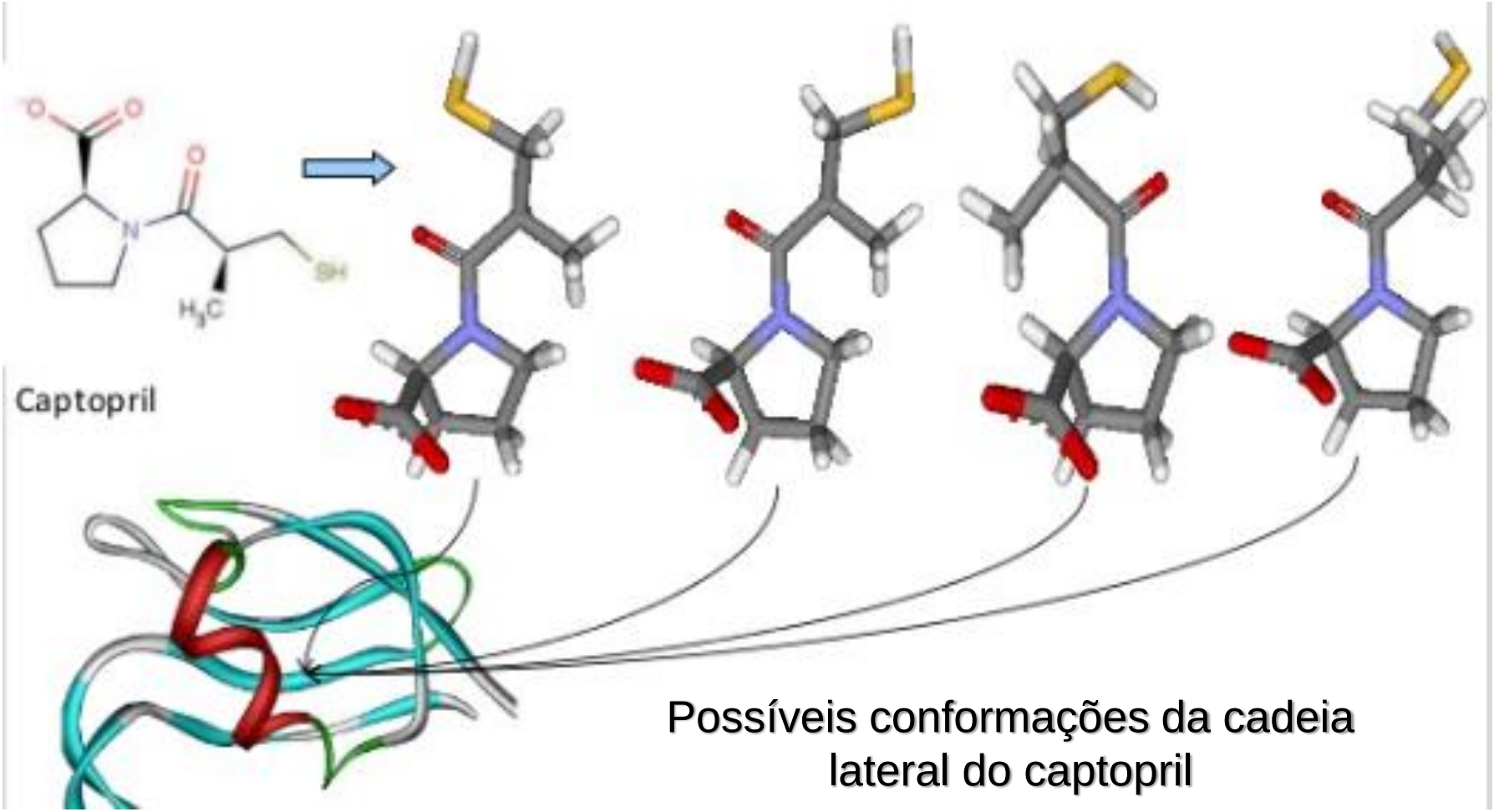
Entre um escritor e um arista, prefira o último!

peptoides

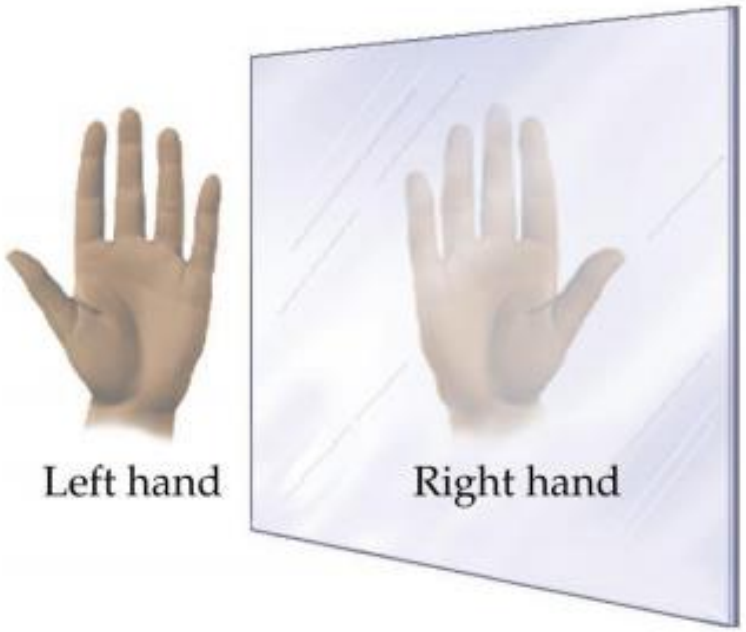

H
N
H
S
CH3
CH3
O
O
N
biciclo
O
OH
amida
Ácido
carboxílico
ciclo
H3C
H
tiol
HS
N
O
HO
O

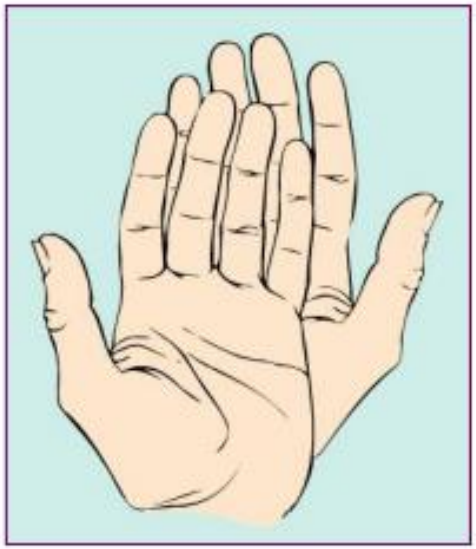


Flexibilidade molecular



Quiralidade



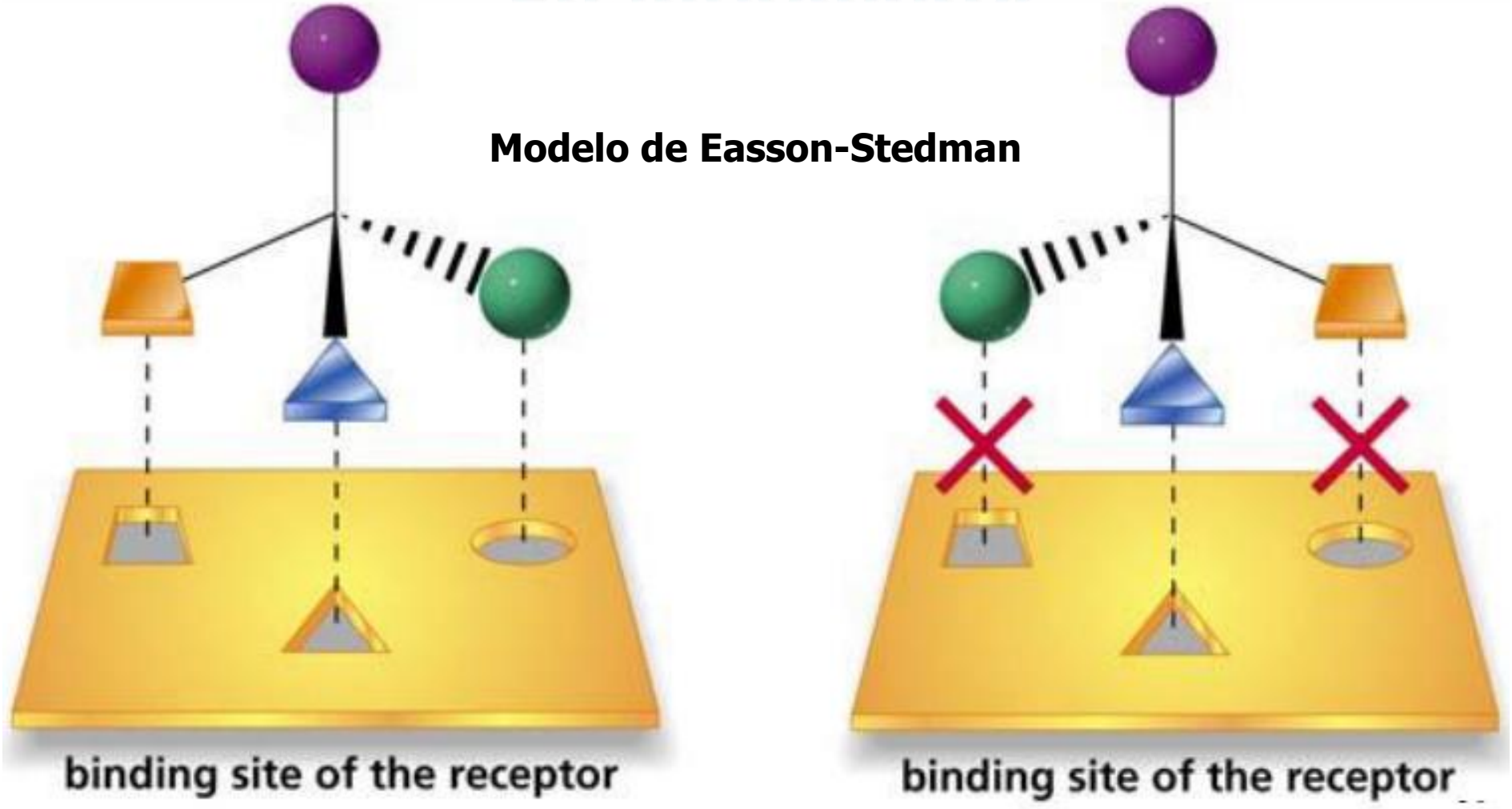


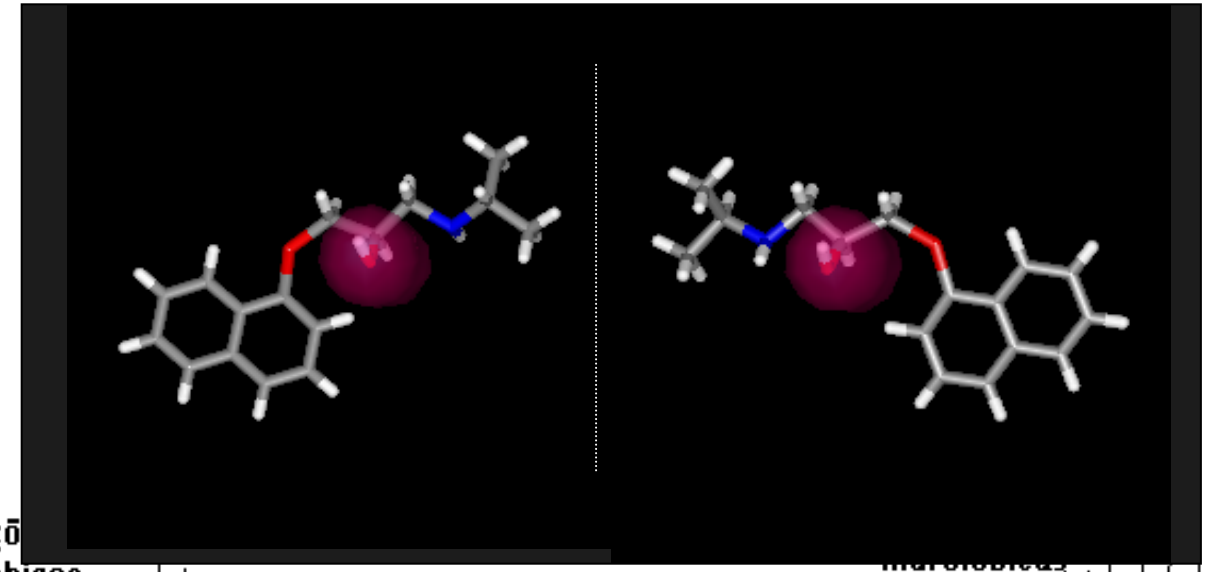
QUIRAL = Cheir (grego) = Mão

Designa corpos e/ou moléculas não sobreponíveis à sua imagem especular.

Enantiomêros

Modelo de Easson-Stedman





Eutômero

Distômero

Interaçõ
hidrofóbicas

estereoespecificidade

(S)

NH_2

COO^-

aspartato

asparagina

(R)

NH_2

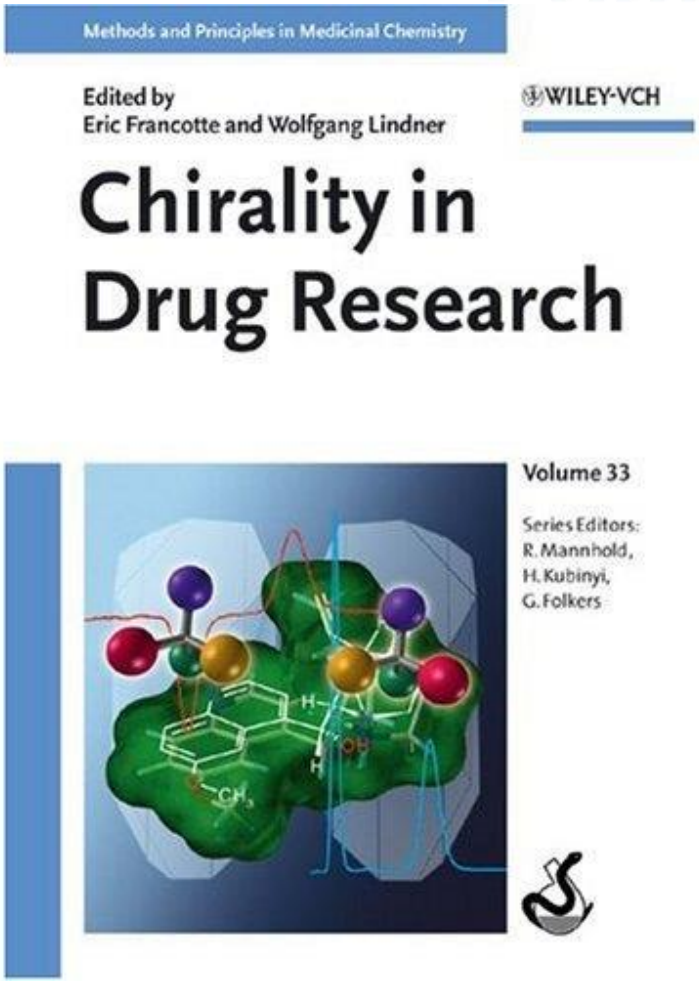
COO^-

asparagina

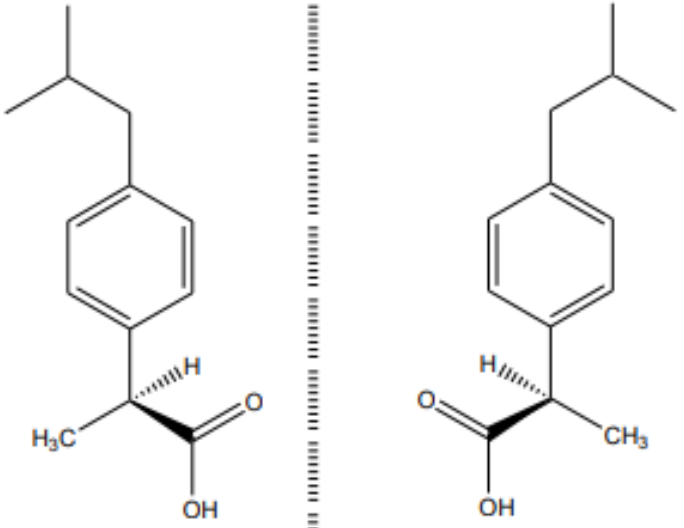
aspartato

Enântiomeros

Configuração



IBUPROFENO

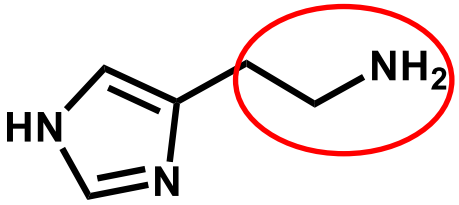


ANTIINFLAMATÓRIO

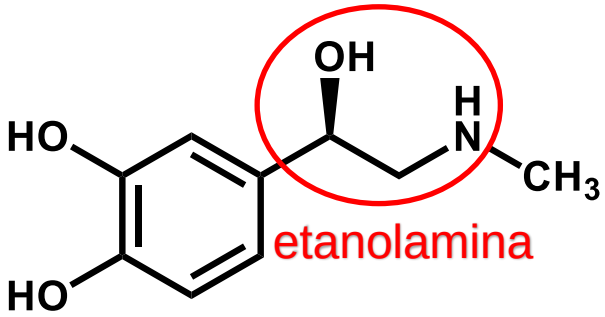
INATIVO

Enantiomêros

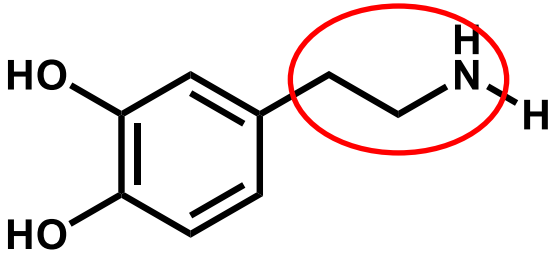
Efeitos conformacionais



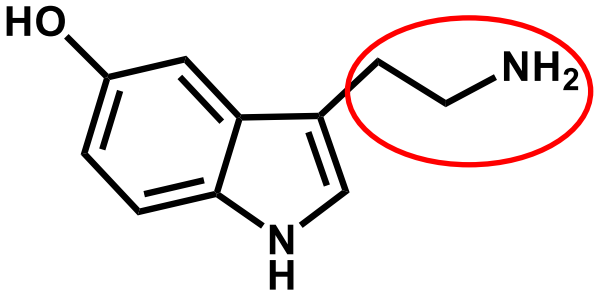
histamina



adrenalina



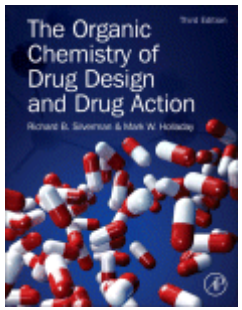
dopamina



serotonina

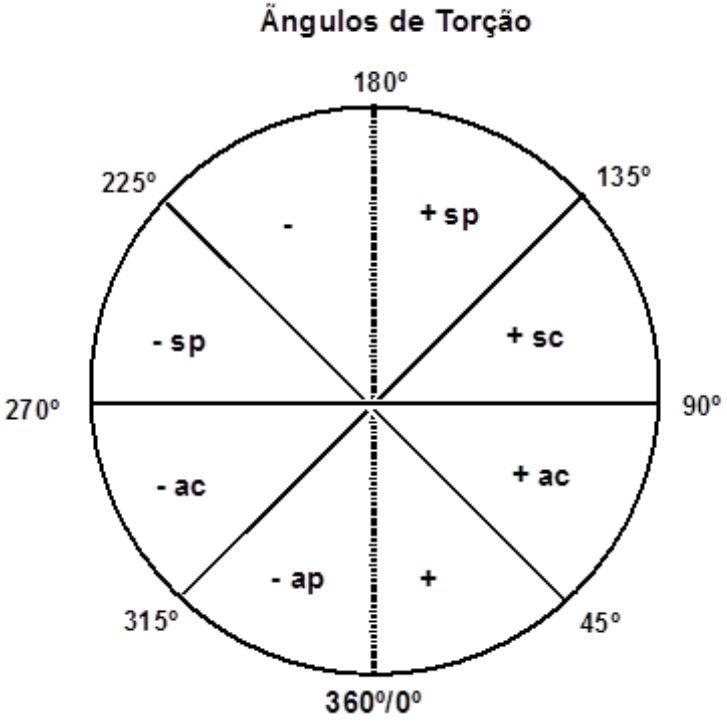
Cap. 4, p. 292

Aminas biogênicas

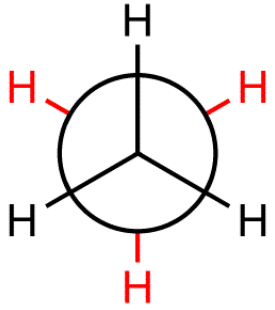


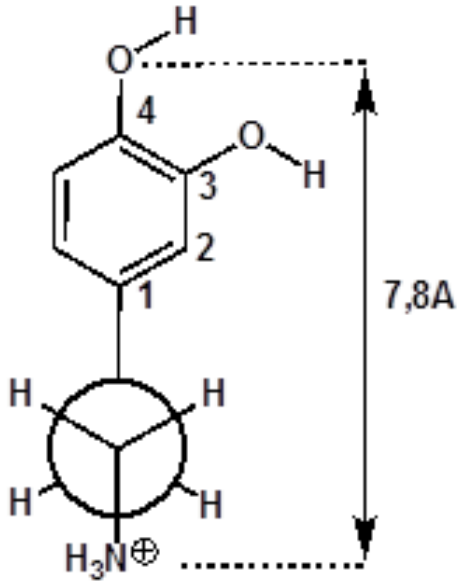
R. B. Silverman, M. W. Holladay, The Organic Chemistry of Drug Design and Drug Action, 3rd Edition, Academic Press, 2014

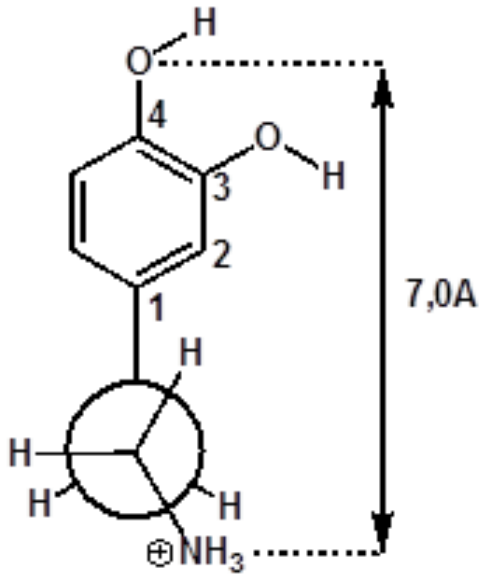
Confôrmeros

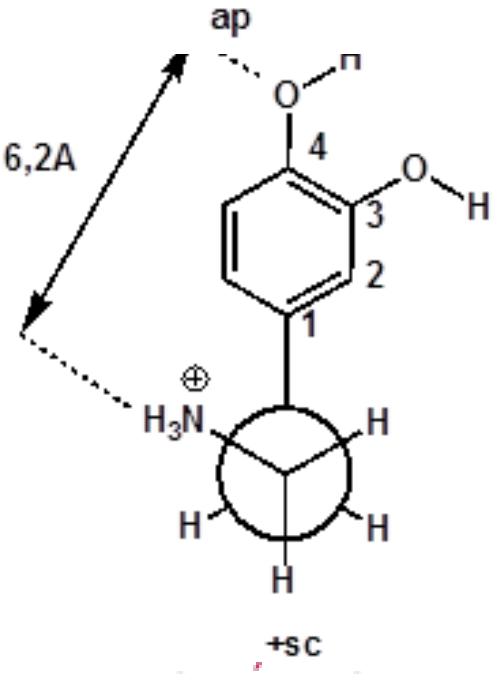


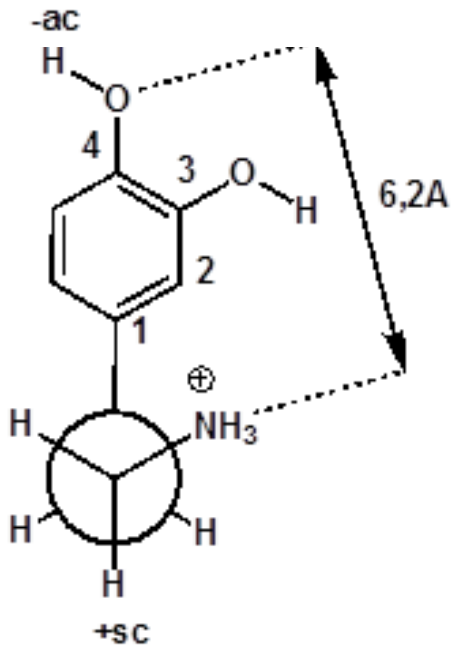
Projeção de Newman





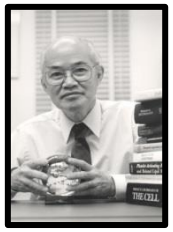




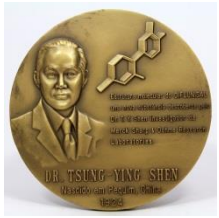


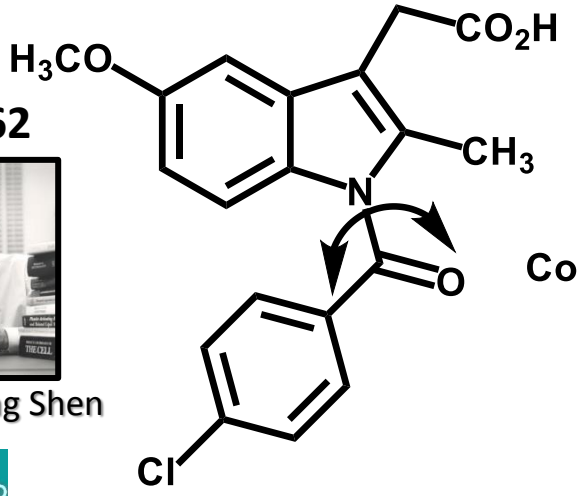
Conformação bioativa

1962

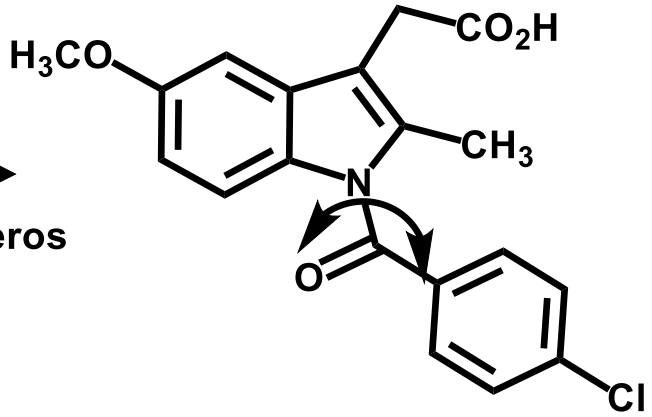


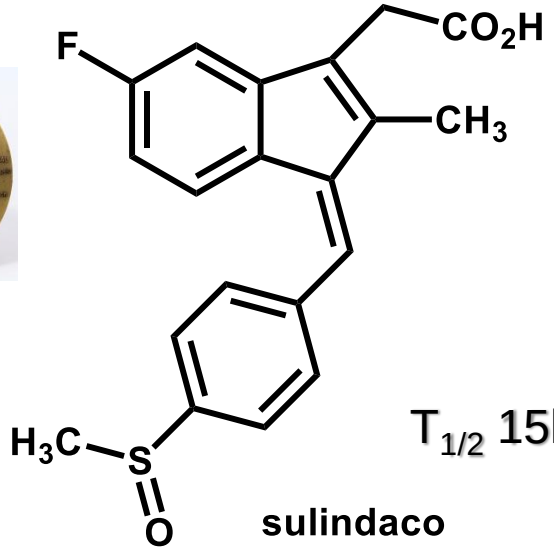
Tsung Ying Shen





Confôrmeros



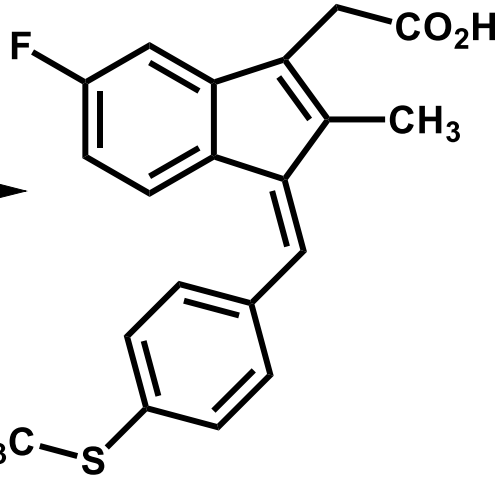


sulindaco

(pró-fármaco)

$T_{1/2}$ 15h

bioativação

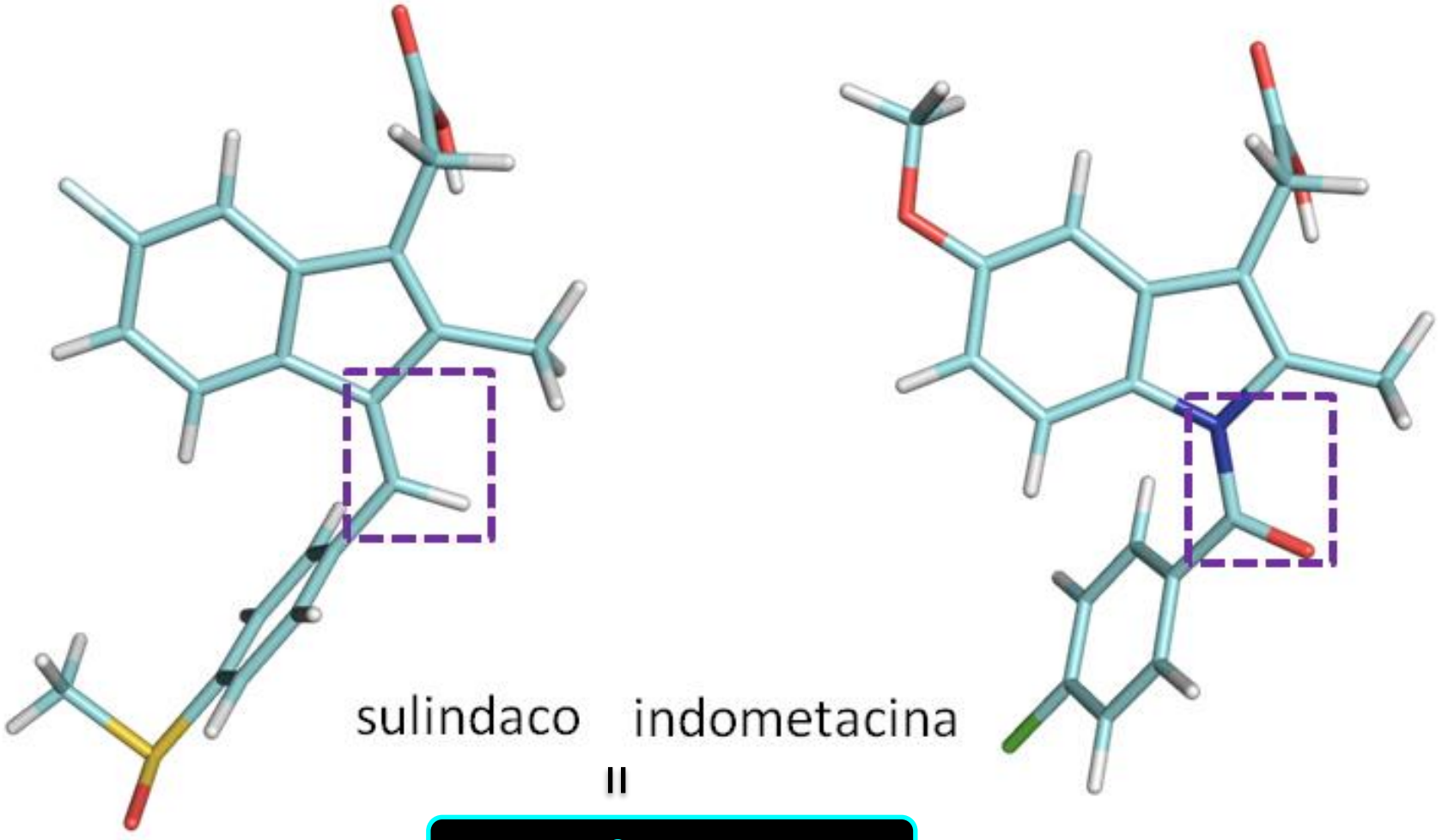


sulindaco-sulfeto

T. Y. Shen et al., *J. Am. Chem. Soc.* **1963**, *85*, 488

T. Y. Shen, Toward more selective antiarthritic therapy, *J. Med. Chem.*, **1981**, *24*, 1

Similaridade molecular

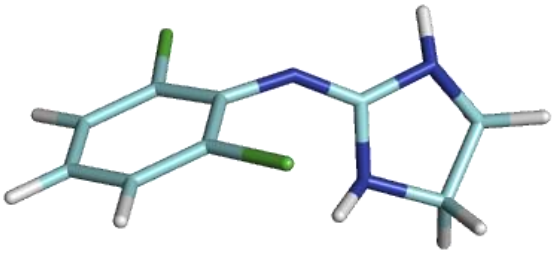


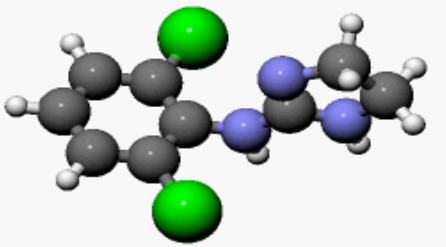
química nova

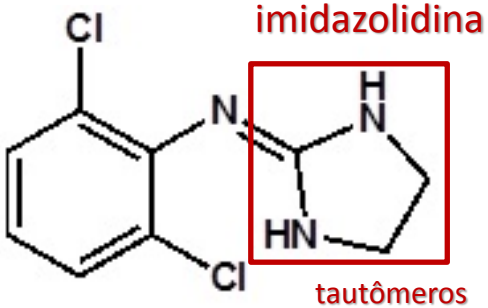
Análogos planejados a partir de produtos naturais brasileiros abundantes (*e.g.* safrol): EJ Barreiro, CAM Fraga, *Quim. Nova* **1999**, *22*, 744

Efeito-*orto* na clonidina

agonista α-$_{2A}$ adrenérgico





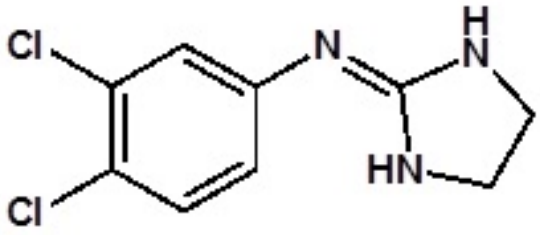


imidazolidina

tautômeros

clonidina

1961

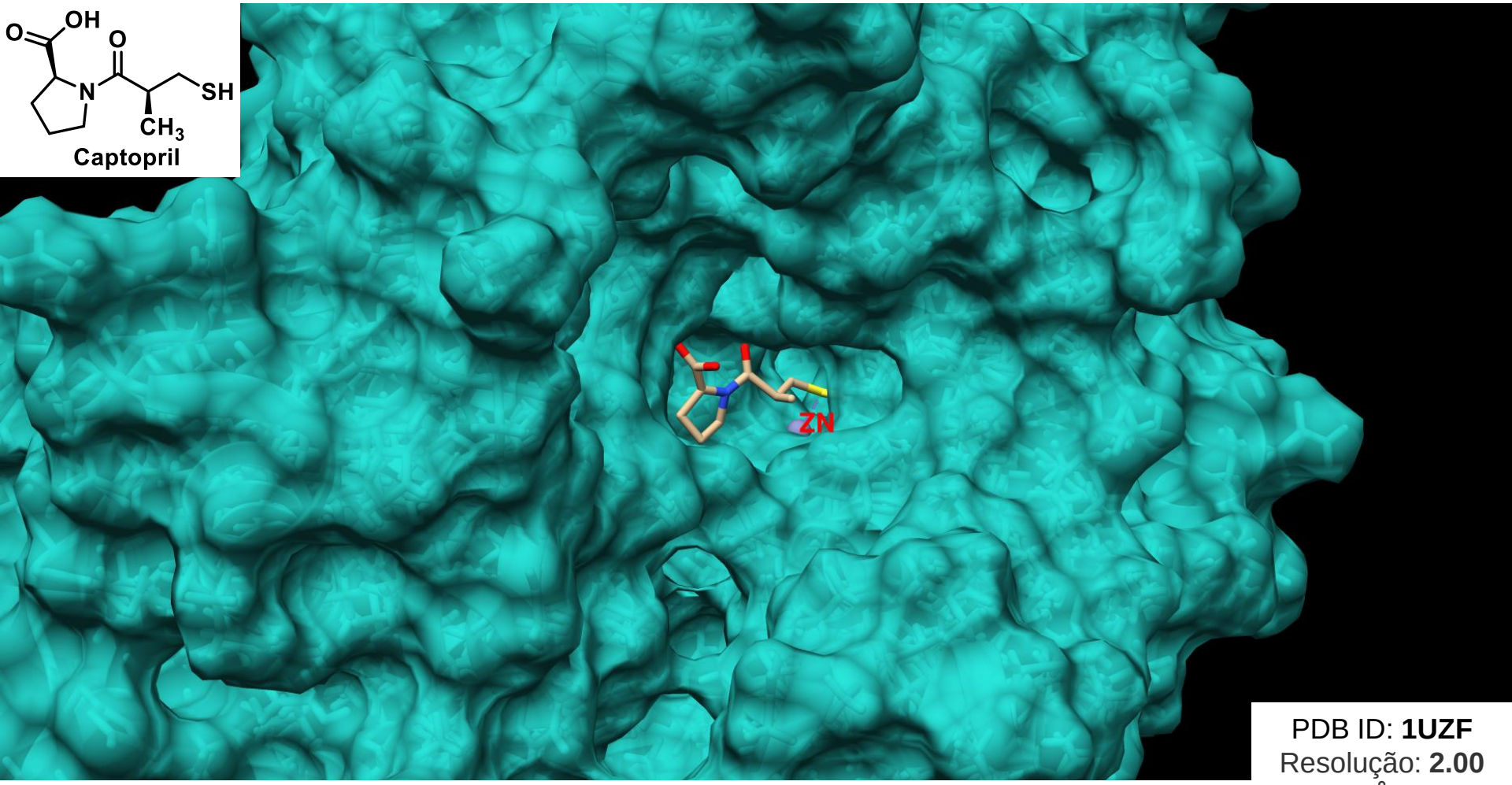


regioisômero

Atividade hipotensora	clonidina	*meta-para*-regio-isômero
ED_{50}	0,1 mg/Kg	3,0 mg/Kg

Receptor	K_i (nM)
α_{1A}	>300
α_{1B}	>300
α_{1D}	>100
α_{2A}	42,92
α_{2B}	106,31
α_{2C}	233,1

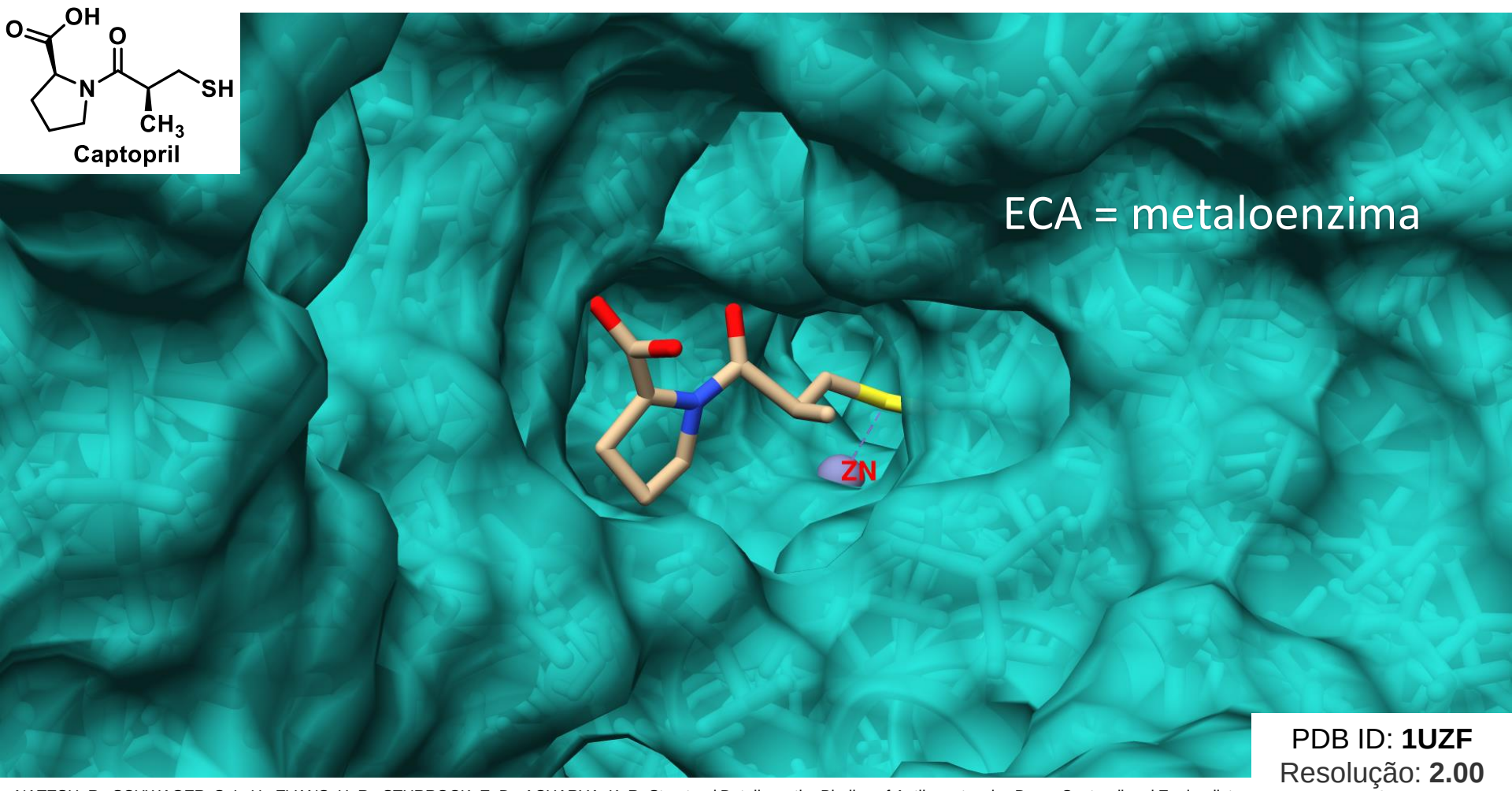
ED_{50} indica atividade *in vivo*



PDB ID: **1UZF**
Resolução: **2.00 Å**

NATESH, R.; SCHWAGER, S. L. U.; EVANS, H. R.; STURROCK, E. D.; ACHARYA, K. R. Structural Details on the Binding of Antihypertensive Drugs Captopril and Enalaprilat to Human Testicular Angiotensin I-Converting Enzyme. **Biochemistry**, v. 43, n. 27, p. 8718–8724, 2004.

Figura de LS Franco, 2021



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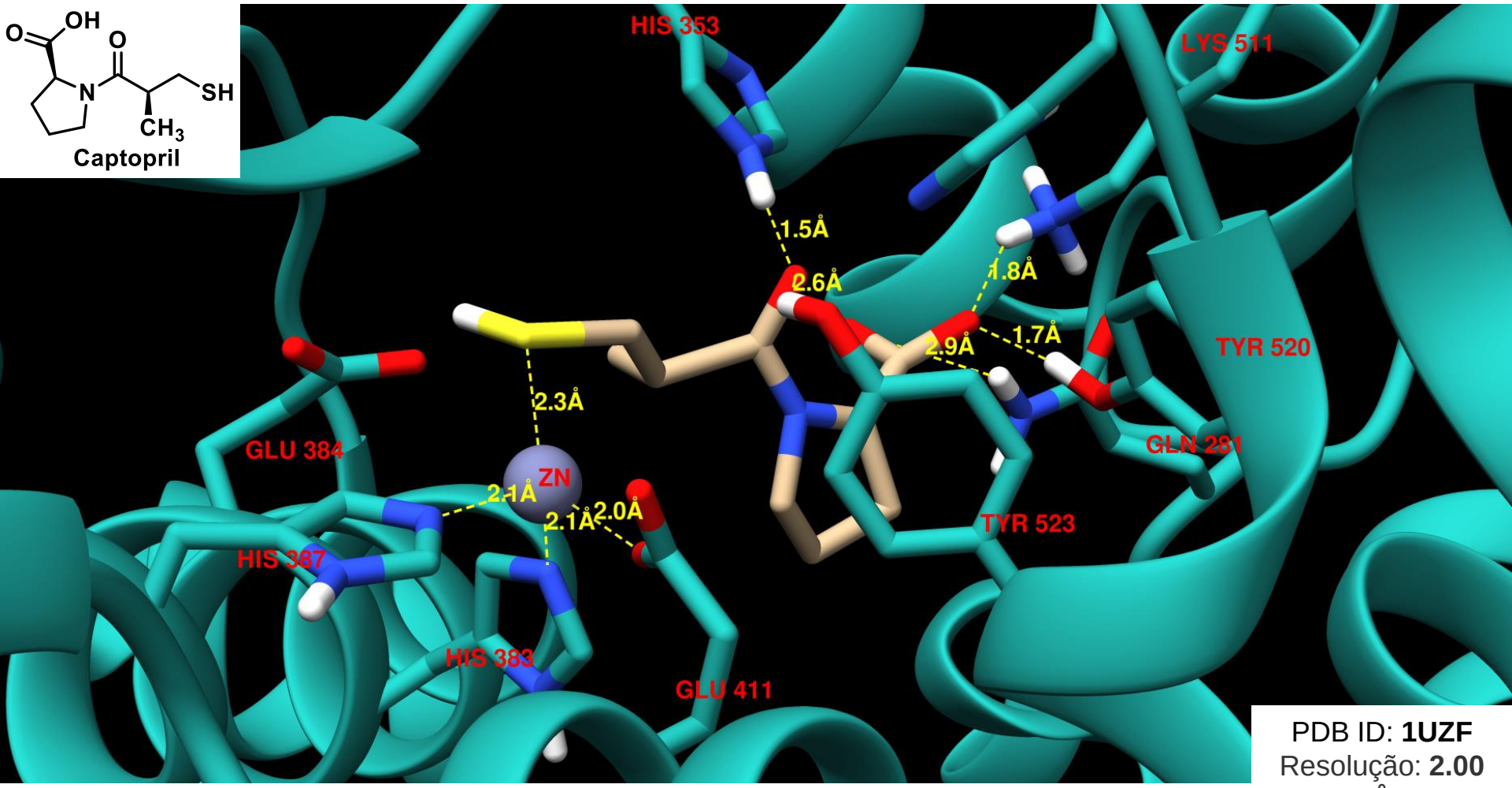

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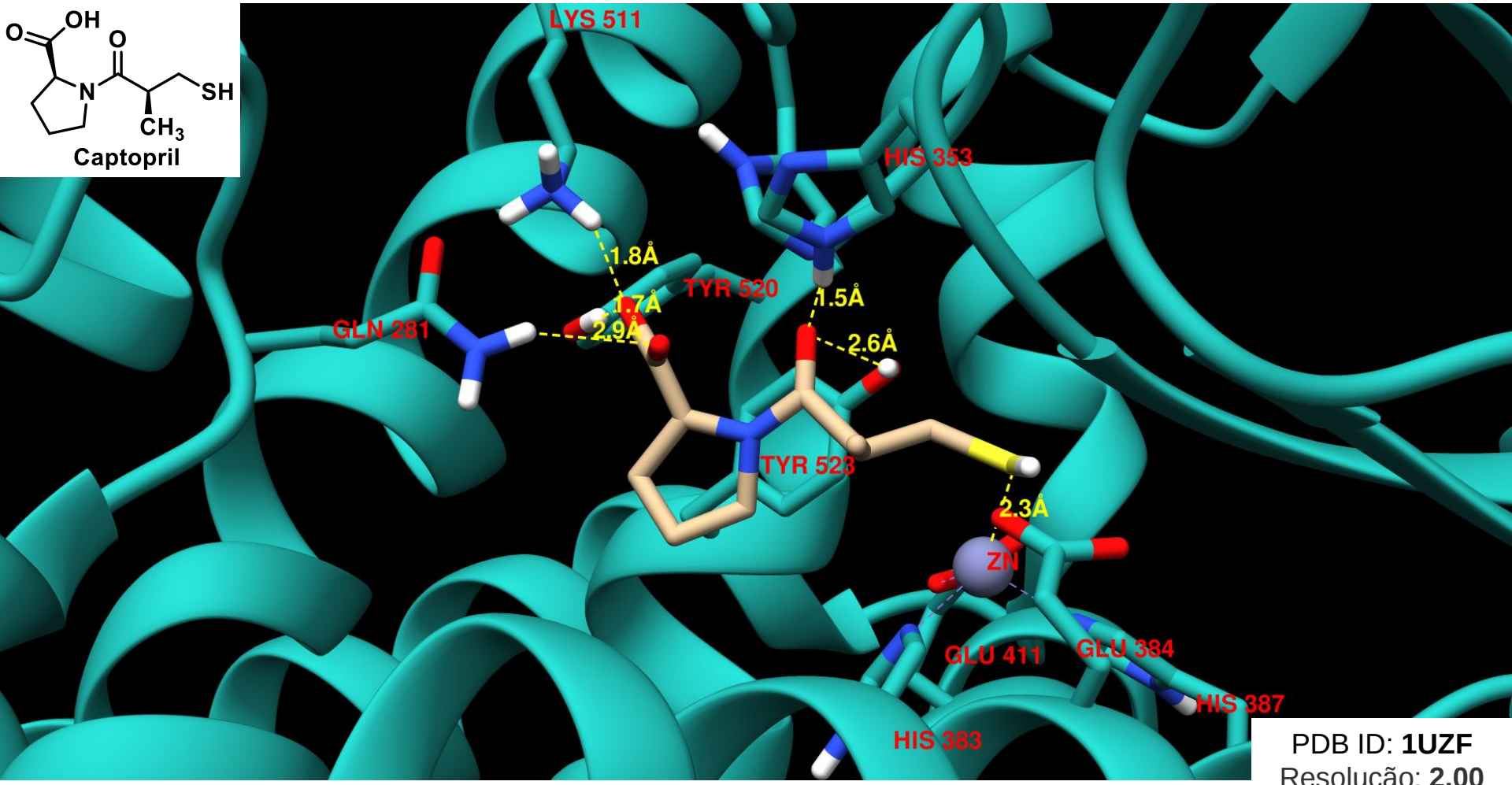

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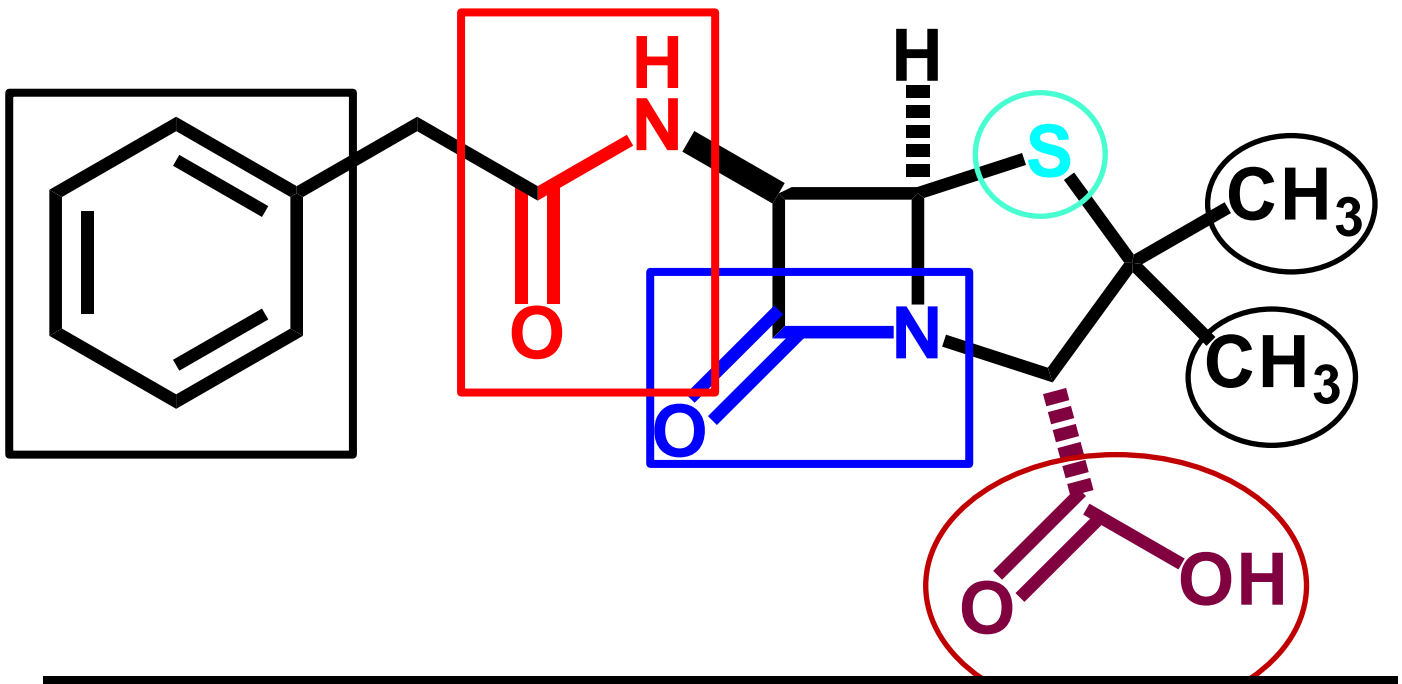
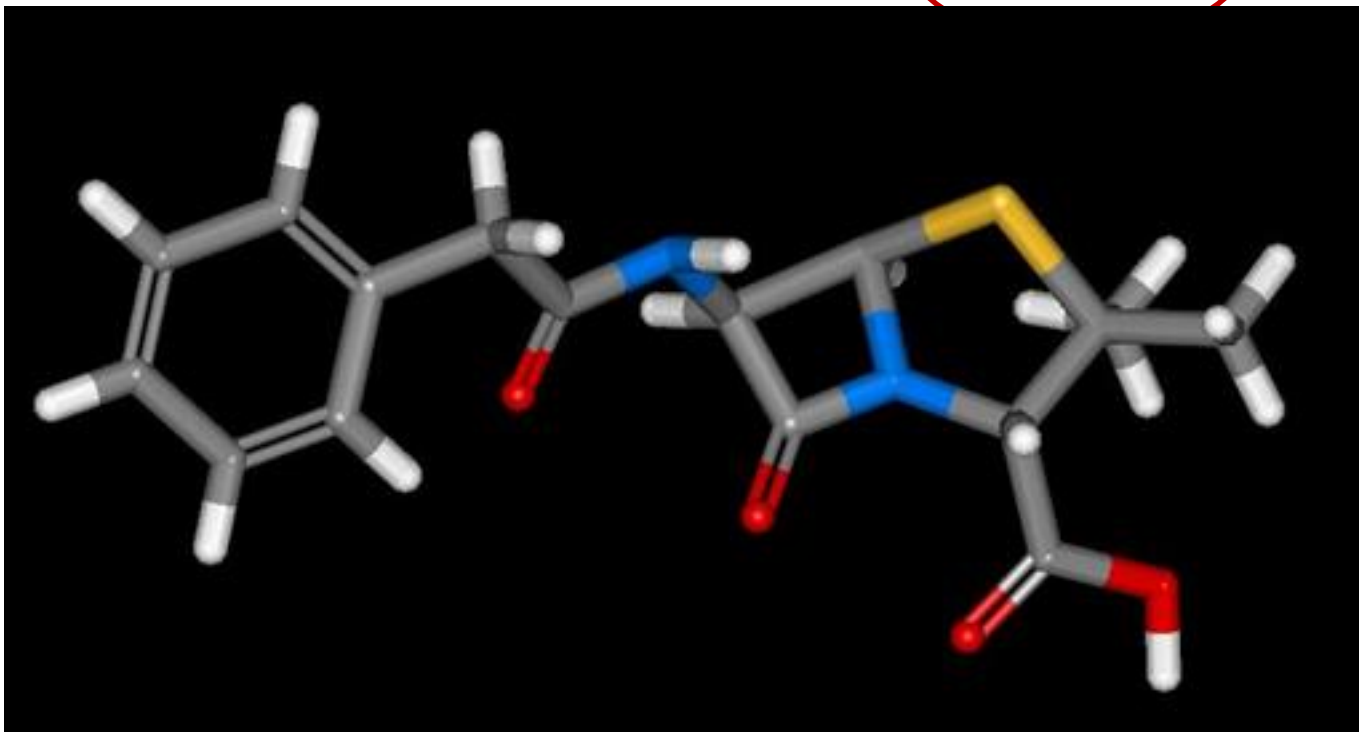
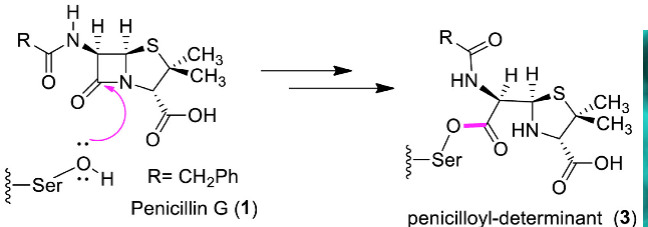
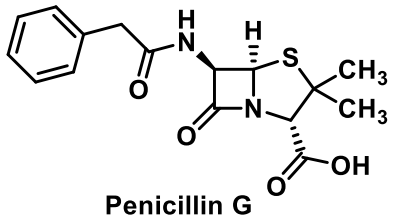

H
N
O
H
S
CH3
CH3
N
O
O
OH





LIMA, L. M.; SILVA, B. N. M. DA; BARBOSA, G.; BARREIRO, E. J. β-lactam antibiotics: An overview from a medicinal chemistry perspective. **Eur. J. Med. Chem.**, v. 208, p. 112829, 2020.



PDB ID: **3UDI**
Resolução: **2.60 Å**

HAN, S.; CASPERS, N.; ZANIEWSKI, R. P.; LACEY, B. M.; TOMARAS, A. P.; FENG, X.; GEOGHEGAN, K. F.; SHANMUGASUNDARAM, V. Distinctive Attributes of β-Lactam Target Proteins in Acinetobacter baumannii Relevant to Development of New Antibiotics. **J. Am. Chem. Soc.**, v. 133, n. 50, p. 20536–20545, 2011.

Figura de LS Franco & RC Maia, 2021

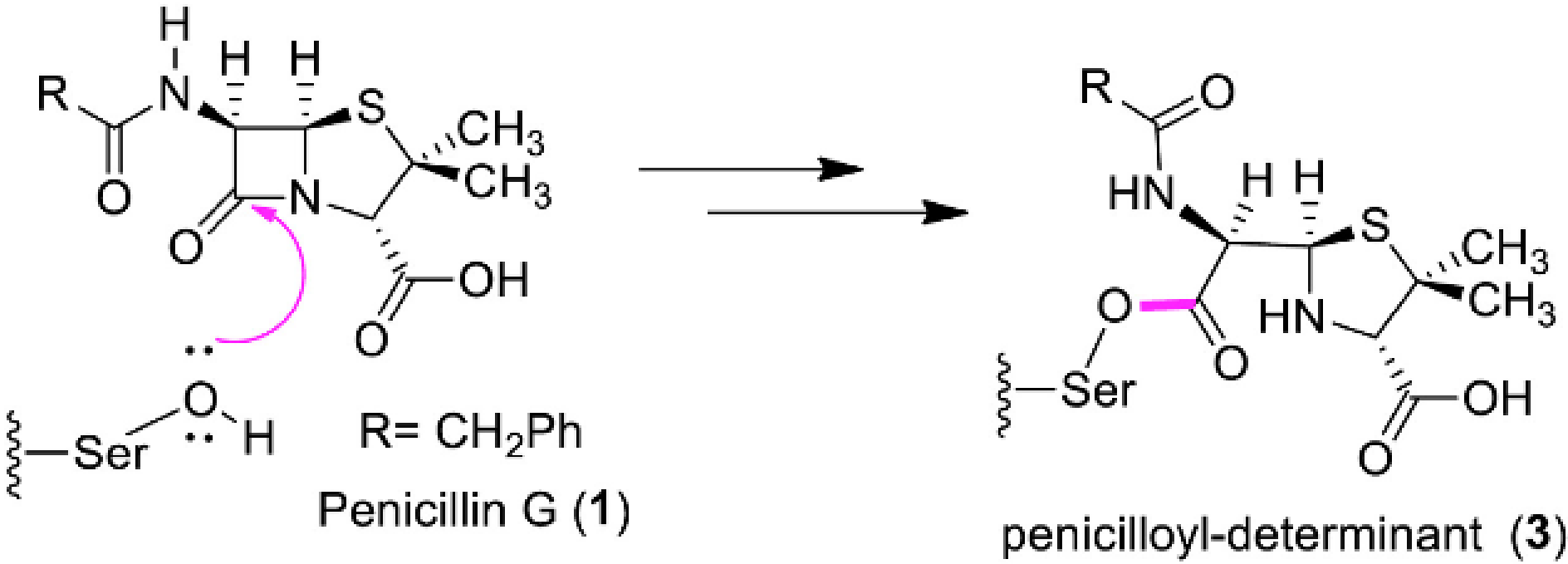


Fig. 2. Nucleophilic addition of the PBP's serine residue to the carbonyl unit of the β-lactam ring of Penicillin G (1).

PDB ID: **3UDI**
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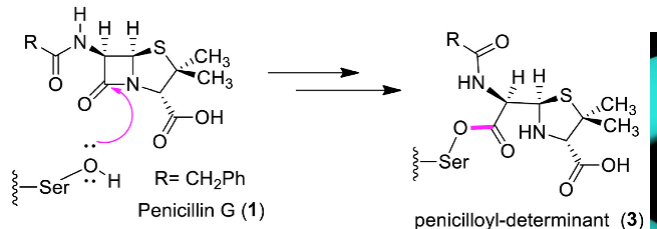

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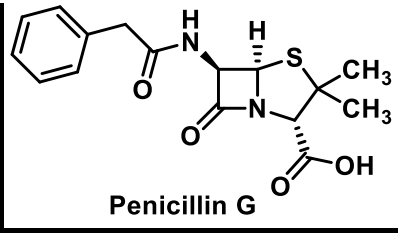

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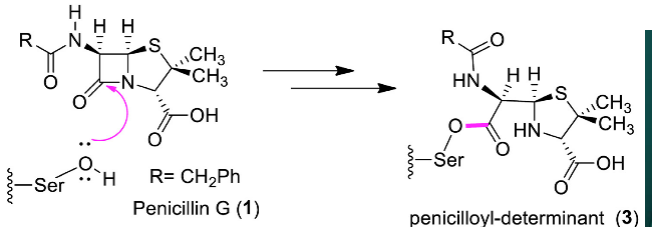

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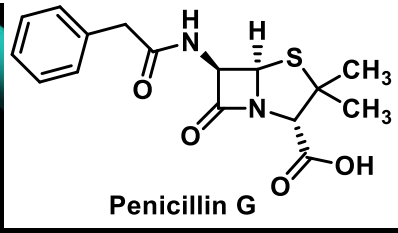

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Figura de LS Franco & RC Maia, 2021

Conceito de Grupo Farmacofórico

Paul Ehrlich (1909) – Um **farmacóforo** "carries (*phoros*) the essential features responsible for a drug's (= pharmacon's) biological activity"
(Ehrlich. *Dtsch. Chem. Ges.* 1909, 42: p.17).

Em 1977, **Peter Gund** atualizou a definição: "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity"
(Gund. *Prog. Mol. Subcell. Biol.* 1977, 5: pp 117–143).

Barreiro & Fraga: **É o conjunto de características eletrônicas e estéricas que caracterizam um ou mais grupos funcionais ou subunidades estruturais, necessários ao melhor reconhecimento molecular pelo receptor e, portanto, para o efeito farmacológico desejado**. Farmacóforo não é uma molécula real, nem associações de grupos funcionais; ao contrário, é um conceito abstrato que representa as diferentes capacidades de interações moleculares de um grupo de compostos com o sítio receptor. O farmacóforo pode ser considerado como a "*parte*" molecular do fármaco essencial à atividade desejada.

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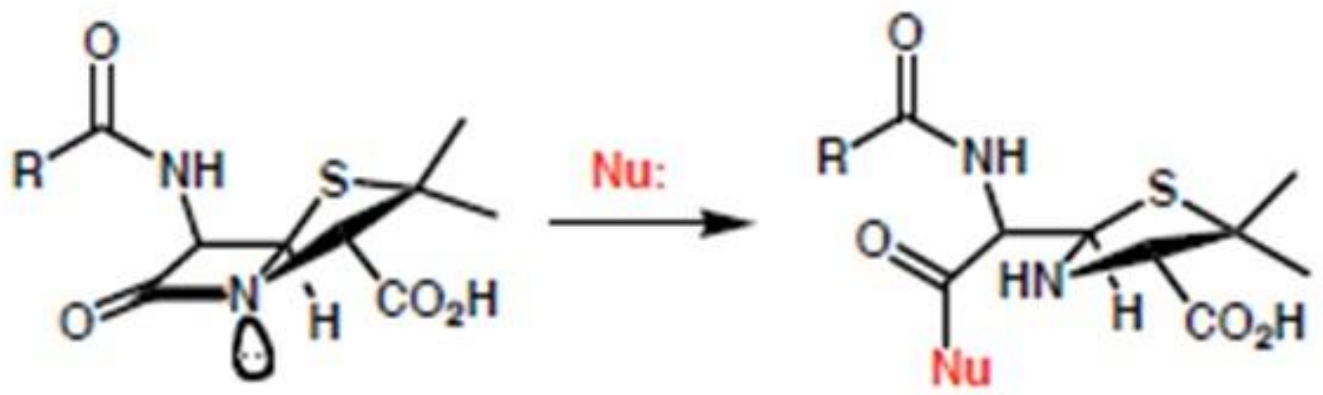
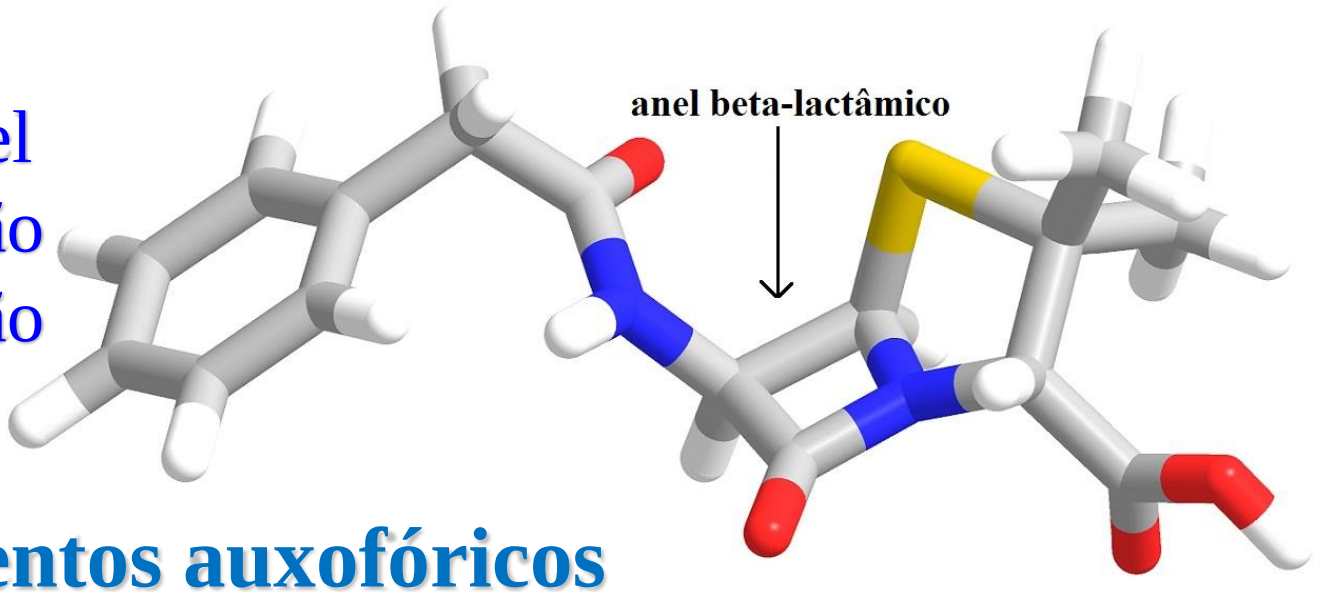
O sistema β-lactâmico



anel beta-lactâmico
de conformação
piramidal definida

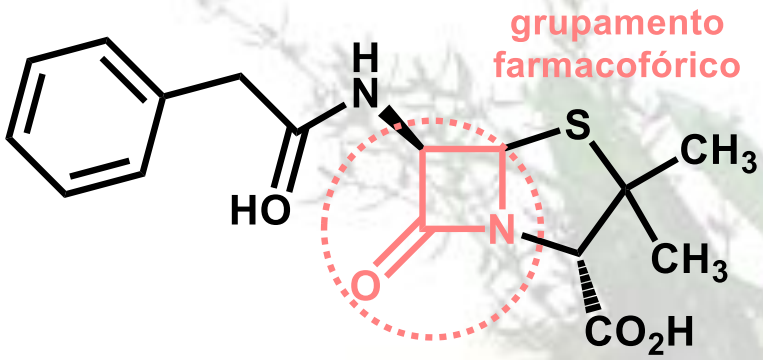
Grupamento farmacofórico

Via Injetável
Conformação
Configuração

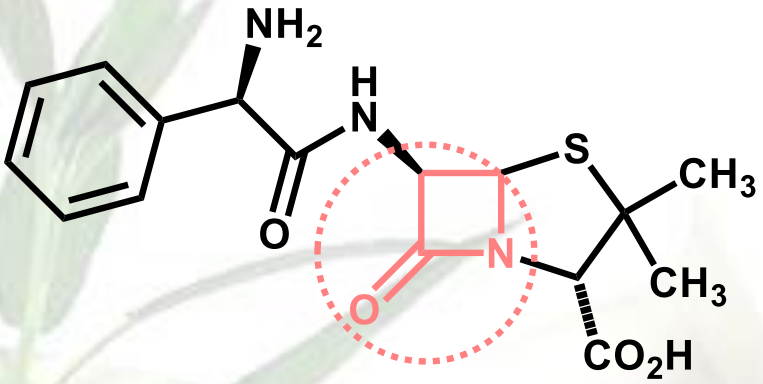


Grupamentos auxofóricos

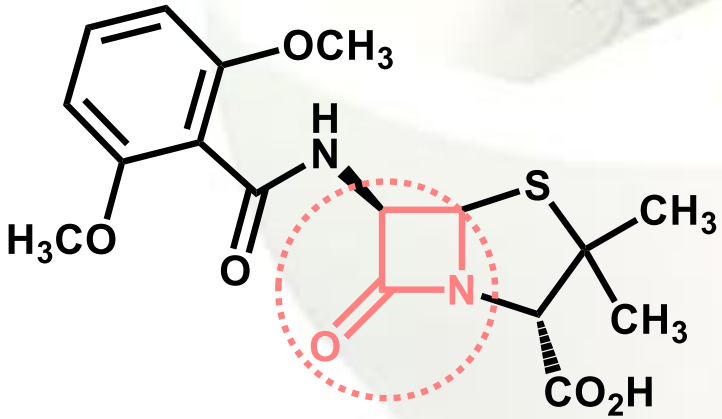
A evolução dos β-lactâmicos...



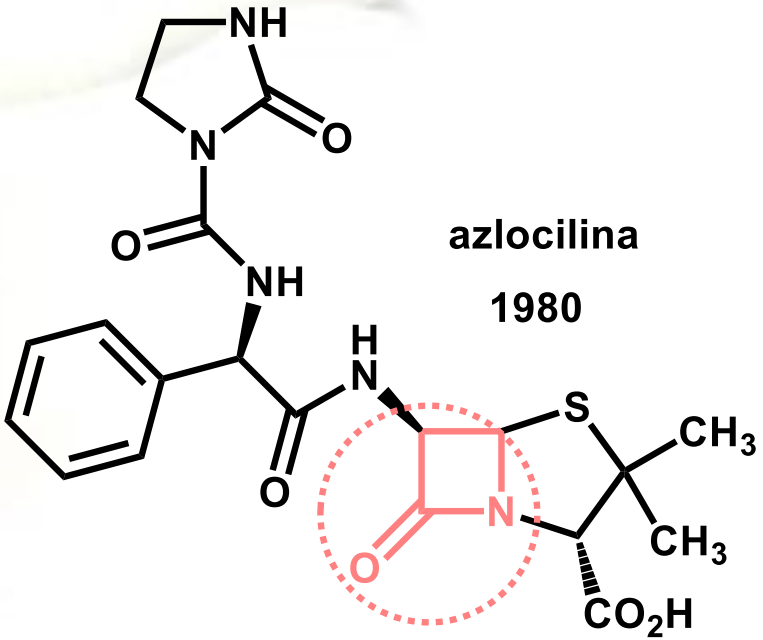
penicilina-G
1942



ampicilina
1958



meticilina
1960



azlocilina
1980