Universidade Federal do Rio de Janeiro

XXVIII Escola de Verão em Química Farmacêutica e Medicinal

25-28 de janeiro de 2022

https://www.evqfm-ufrj.org/

Curso 3

Estruturas privilegiadas no desenho de fármacos

Parte 1

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Programa de de Pós-Graduação em Farmacologia e Química Medicinal

www.inct-inofar.ccs.ufrj.br

www.lassbio.icb.ufrj.br

Estruturas privilegiadas

Este mini-curso

Neste **curso-curto** (6h), tratar-se-á da questão das estruturas privilegiadas no desenho de novas pequenas moléculas, candidatas a novos fármacos não-proteicos (nem biotecnológicos).

"pequenas moléculas, grandes curas"

Química Medicinal

MINICURSO 3 : Estruturas privilegiadas no desenho de fármacos

Prof. Eliezer J. Barreiro

LASSBio, ICB, UFRJ

XXVIII Escola de Verão em Química Farmacêutica Medicinal Professor Eliezer Barreiro

Ementa: A Química Medicinal tem tido contínua atualização nas estratégias de desenho molecular, como reflexo dos avanços tecnológicos diversos. Dentre as estratégias contemporâneas surgiu a utilização das estruturas privilegiadas. Este termo surgiu em 1988, quando foi empregado por Evans e colaboradores, pesquisador da Merck, na descrição de resultados de simplificação molecular de estruturas complexas de produtos naturais de interesse terapêutico. Inúmeros trabalhos subsequentes adotaram-na com sucesso, validando o termo no glossário de Química Medicinal. Este curso tratará dos aspectos moleculares de estruturas privilegiadas selecionadas consideradas como sendo moleculas presentes em vários fármacos, de diferentes indicações terapêuticas, atuando em biorreceptoeres ou enzimas distintas.
As propriedades moleculares das estruturas privilegiadas selecionadas para discussão, compreenderão os aspectos farmacodinâmicos e farmacocinéticos, com exemplos ilustrativos. Dentre estes, incluiremos alguns de casa.

Bibliografia:

L Yet, Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis, Wiley, 2018 (ISBN:9781118145661);

S. Bräse, Privileged scaffolds in medicinal chemistry, Design, Synthesis Evaluation, RSC Drug Discovery #50, 2016 (ISBN: 978-1-78262-030-3).

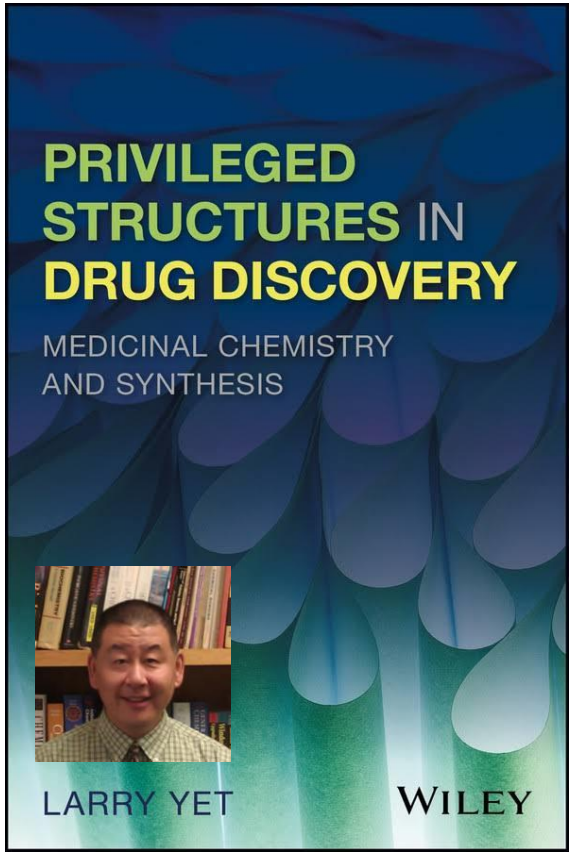
http://ejb-eliezer.blogspot.com/2021/07/as-estruturas-privilegiadas-e-o-desenho.html

Bibliografia

Privileged scaffolds

London, 2016.

Privileged structures



Chapter 1 Privileged Scaffolds in Medicinal Chemistry:
An Introduction 1
Eliezer J. Barreiro

Inter-alia: Privileged structures; privileged scaffolds; privileged fragments; privileged core; chemotype; molecular fragment;

De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. História da descoberta/invenção de fármacos e aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

Química Medicinal

domingo, 25 de julho de 2021

As estruturas privilegiadas e o desenho de novos fármacos...

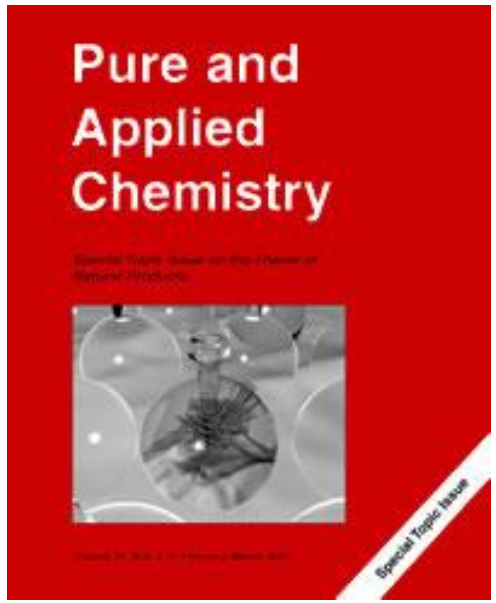
Há pouco tempo, precisamente em 2019, publiquei um artigo com dois orientandos como coautores (e.g. Lucas Franco e Júlia Pedreira), sobre o papel da intuição em química medicinal. Foi uma ótima experiência em que o "produto final" foi fruto do trabalho de 6 mãos e 3 cabeças...! Mas só uma "branquinha"...!!!! (Veja: JGB Pedreira, LS Franco, EJ Barreiro, Chemical Intuition in Drug Design and Discovery, Curr Top Med Chem 2019, 19, 1679).

www.ejb-eliezer.blogspot.com

IUPAC - Subcommittee Medicinal Chemistry & Drug Development

Química Farmacêutica Medicinal

Definição: Química Medicinal é a



disciplina que estuda os aspectos relacionados à *descoberta* ou *invenção* dos fármacos, os aspectos moleculares envolvidos em seu mecanismo de ação e aqueles que governam a *absorção*, *distribuição*, *metabolismo*, *eliminação* e *toxicidade* (ADMET), incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica (REA; SAR).

Química Medicinal

IUPAC

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

Eur. J. Med. Chem., *31*, 747 (1996)

O processo de *drug discovery*

Eleição do alvo terapêutico

Composto protótipo — Desenho

Biodisponibilidade — ADMET*

Fase Pré-Clínica — GLP

Farmacologia clínica — Ensaios clínicos

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

Doença

Química Medicinal

*ADMET = Absorção; Distribuição; Metabolismo; Eliminação; Toxicidade

Pesquisa

Abordagem fisiológica

Química med Medicinal chem

Propriedade intelectual

Modelo Linear

Desenvolvimento

Métodos analíticos quantitativos

Métodos analíticos qualitativos

Métodos bioquímicos

Desenvolvimento farmacotécnico

GLP / GMP

Scale-up

Informatização do processo

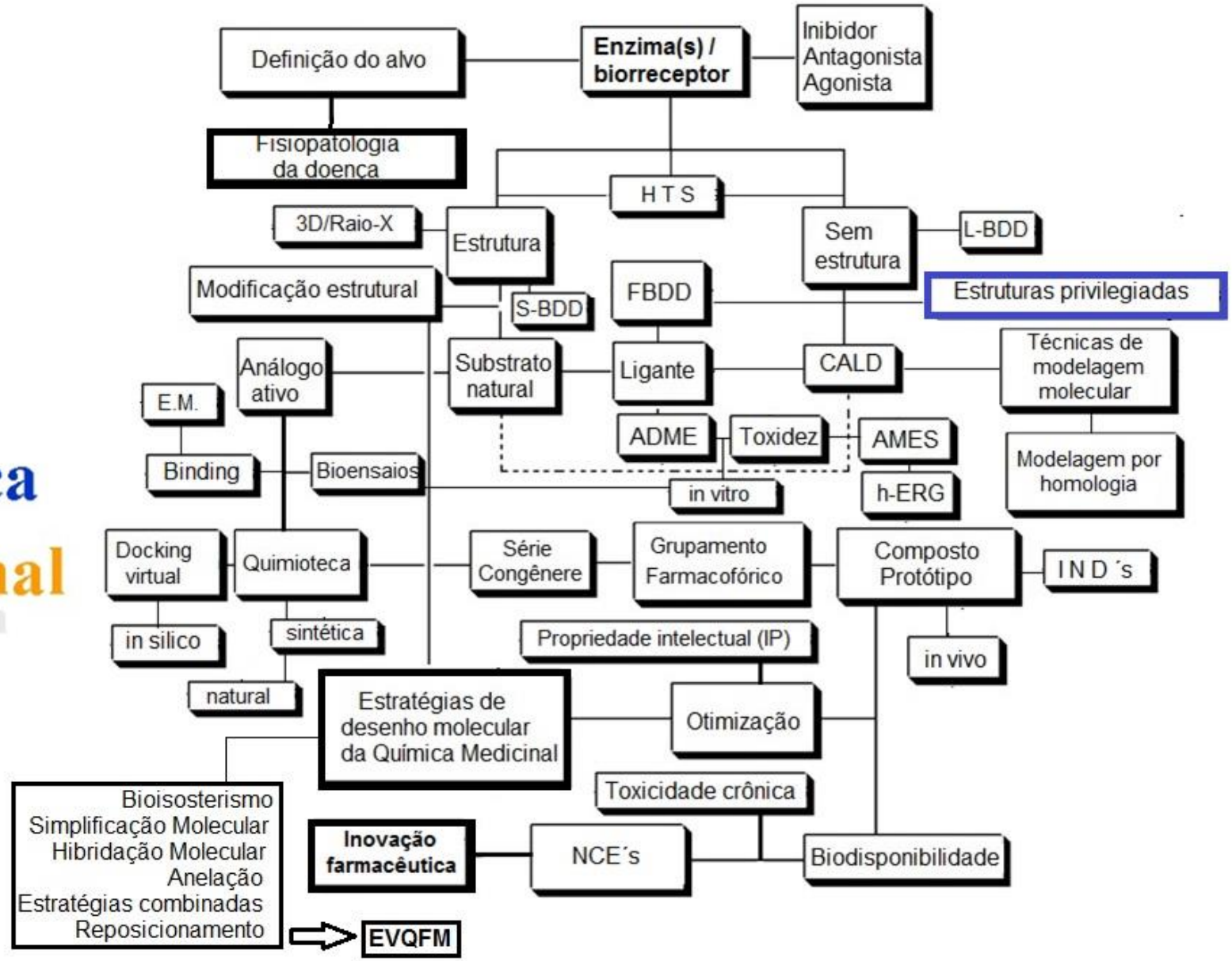
Práticas de produção

Normas regulatórias

Fabricação

Licenciamento

Comercialização



Química med Medicinal chem

ADME = absorção, distribuição, metabolismo, eliminação (inclui estabilidade química e metabólica; AMES = teste de mutagenicidade; CALD = *computer assisted ligand design;* FBDD = *fragment-based drug discovery;* *h*-ERG = toxicidade (*human-ether-a-go-go related gene*); HTS = high throughput screening; IND = investigational new drug; L-BDD = ligand-based drug design; NCE = new chemical entity; S-BDD = stucture-besed drug design;

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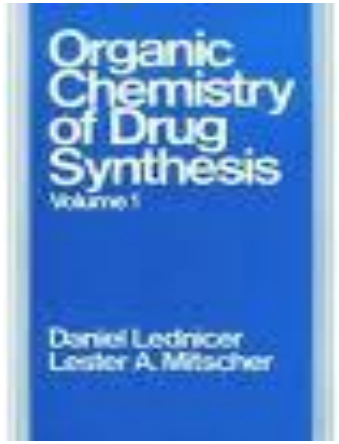
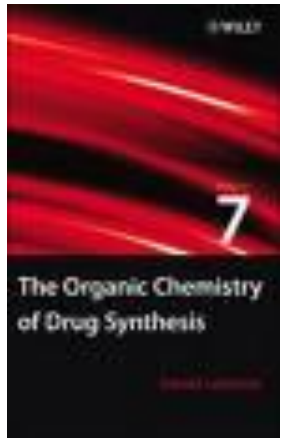
"...The genealogy of quite recently introduced drugs however provides a good illustration of the role that serendipity, ***intuition*** or even pure chance have played in drug discovery up until quite recently."

Daniel Lednicer



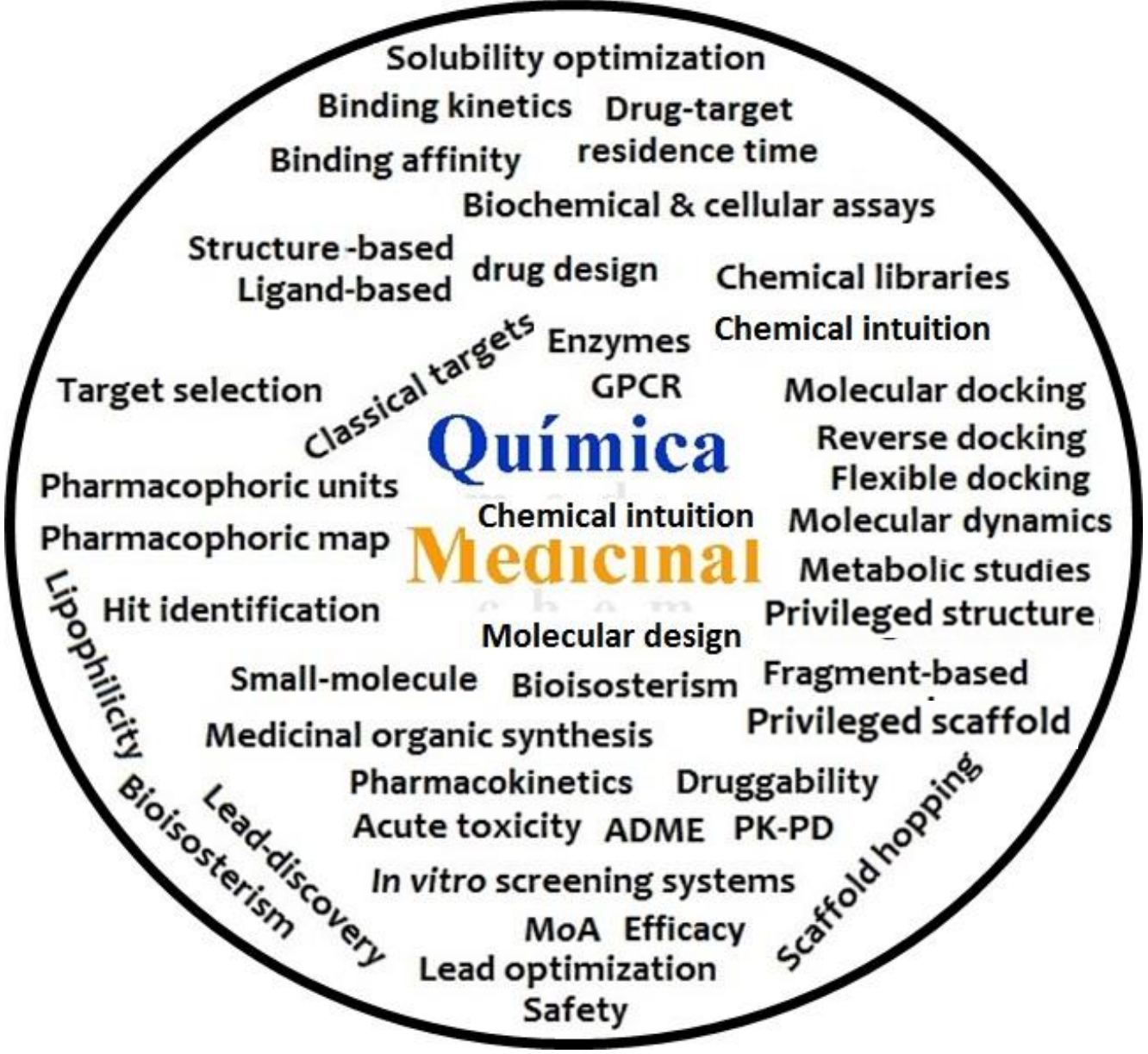
"On the origin of drugs"



"...In drug design, chemical ***intuition*** is an important element..."

James P. Snyder, 1991

Emory University, GA, EUA



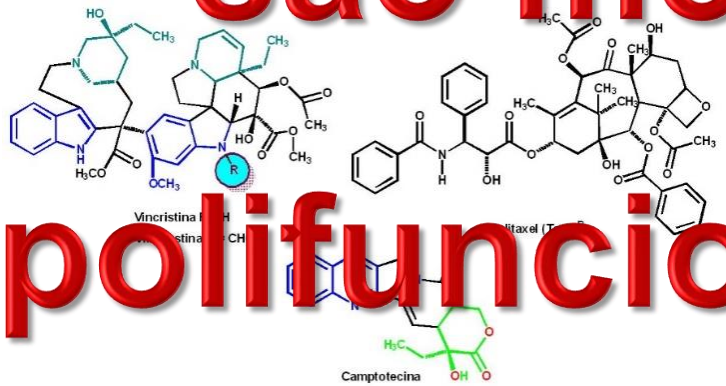
Estruturas Privilegiadas

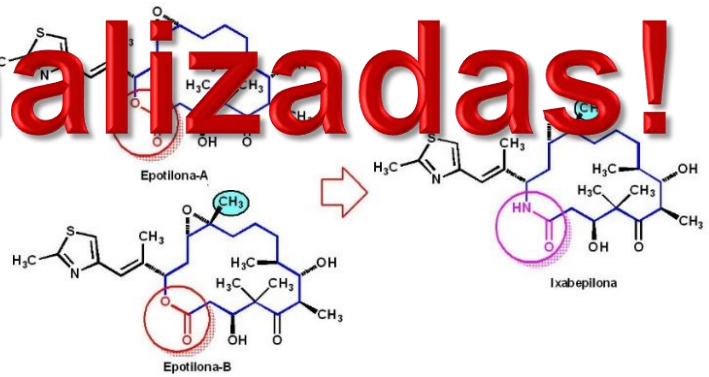
J.G.B. Pedreira, L. S. Franco, E. J. Barreiro, Chemical Intuition in Drug Design and Discovery, *Current Topics in Medicinal Chemistry* **2019**, *19* (19), 1679.

https://doi.org/10.2174/1568026619666190620144142

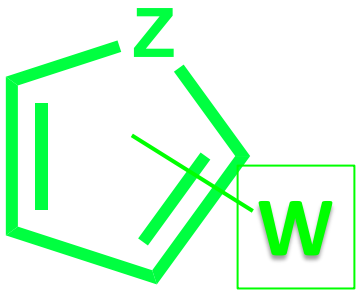
Drug Discovery

Os fármacos são moléculas polifuncionalizadas!



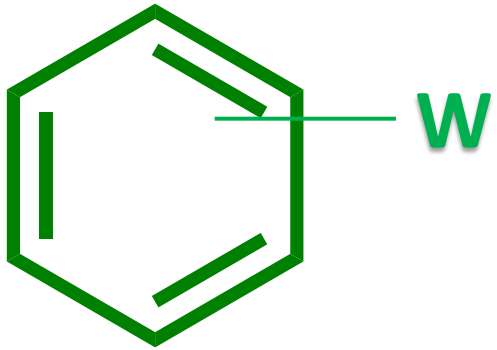


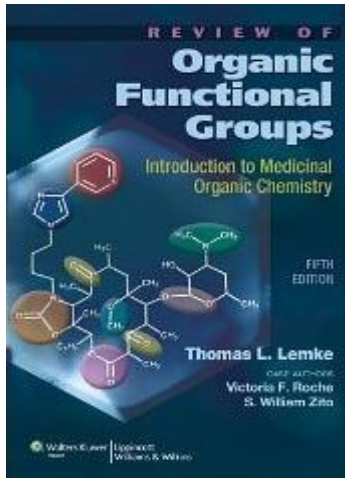
Scaffolds mais comuns nas moléculas dos fármacos



Z = NH, O, S

Os mais frequentes…





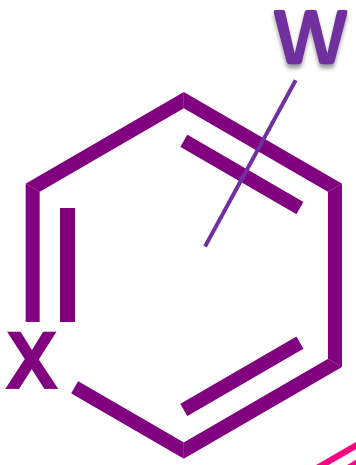
[Curso XXV EVQFM Parte 1]

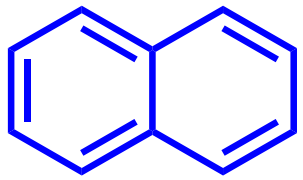
[Curso XXV EVQFM Parte 2]

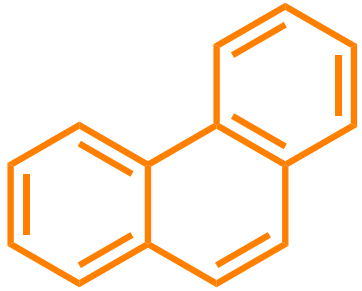
Propriedades eletrônicas

6, 10, 14, 18 π

X = N

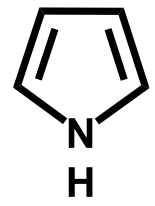


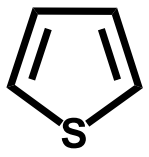


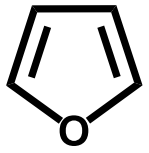


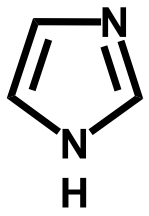
50% do fármacos atuais contêm pelo menos um *anel aromático*, capaz de sofrer substituições.

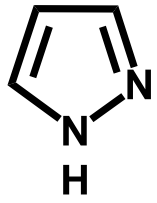
Diversidade molecular

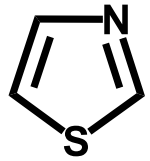

Pirrola

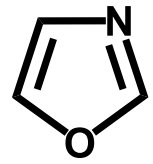

Tiofeno

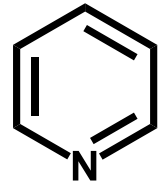

Furana

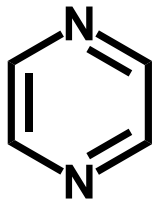

Imidazola


Pirazola


Tiazola


Oxazola


Piridina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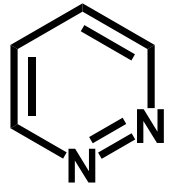
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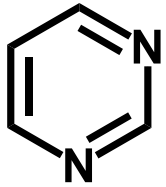
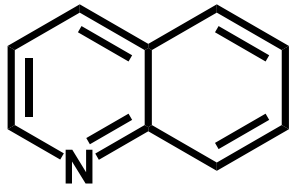
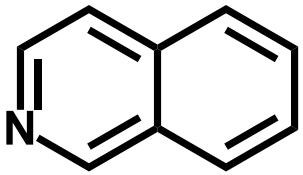
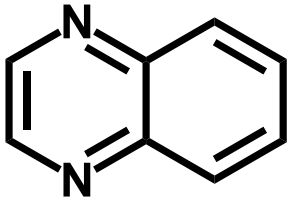
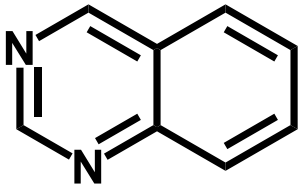
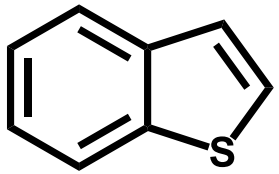

Pirimidina

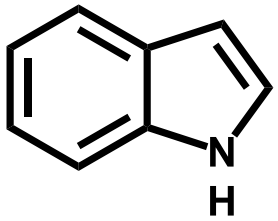

Quinolina

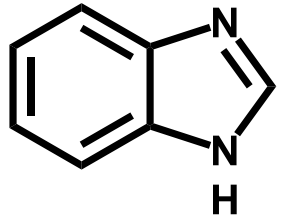

Isoquinolina

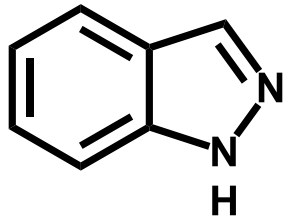

Quinoxalina

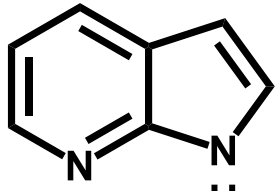

Quinazolina

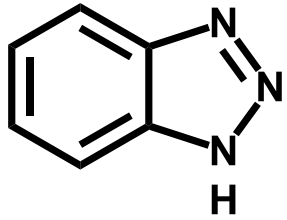

Benzotiofeno

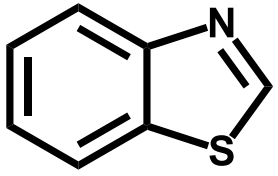

Indol

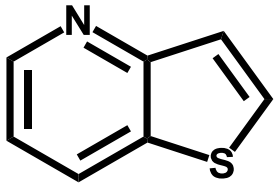

Benzimidazola

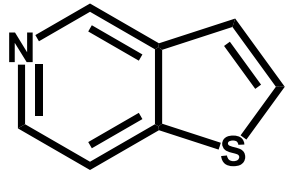

Indazola

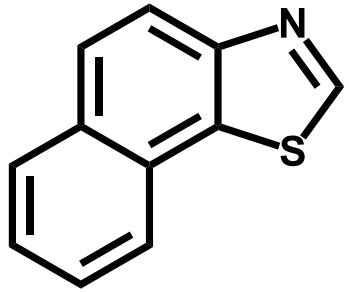

7-aza indol

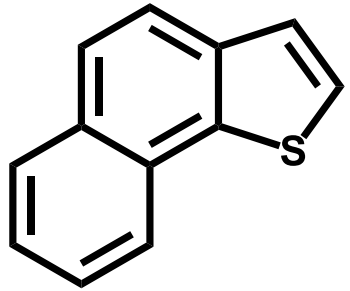

1*H*-Benzotriazola


Benzotiazola

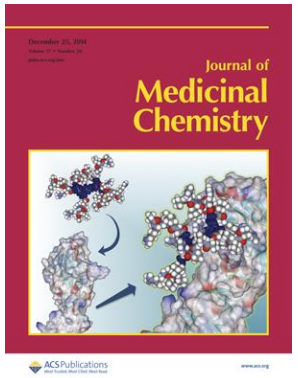

Tieno[3,2-*b*]piridina


Tieno[3,2-*c*]piridina


Nafto[2,1-*d*]tiazola


Nafto[1,2-*b*]tiofeno

E Vitaku, D T Smith, J T Njardarson, Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals, *J Med Chem* **2014**, *57*, 10257



1994

U.S. FDA approved drugs

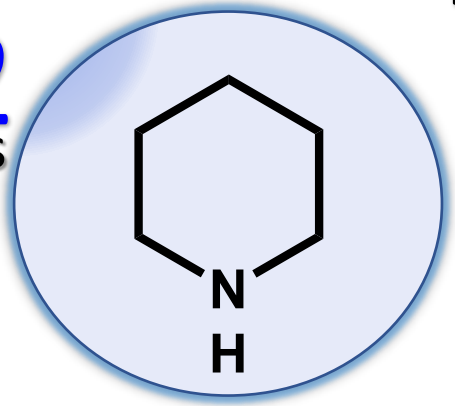
1086 *Pequenas moléculas*

640 *N*-heterocíclicos

59%

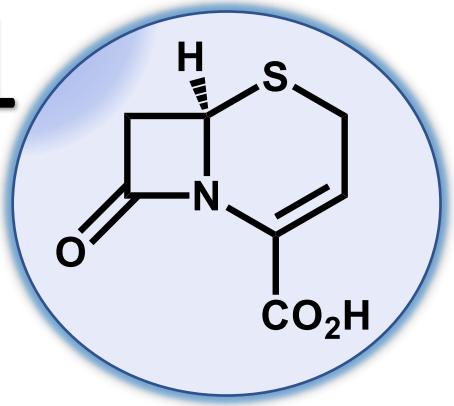
72 fármacos

piperidina



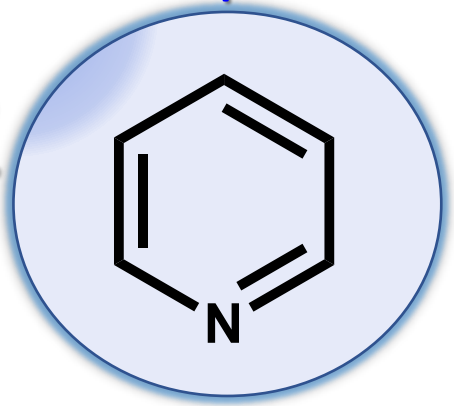
cefem

41



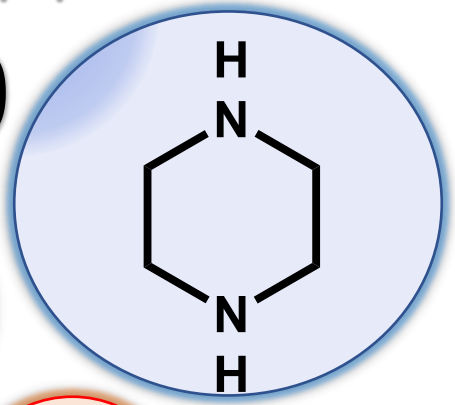
piridina

62



piperazina

59



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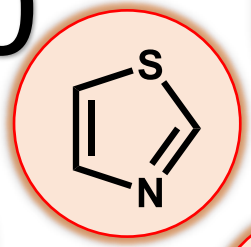

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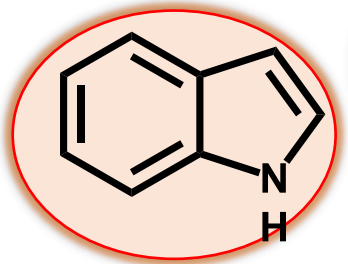

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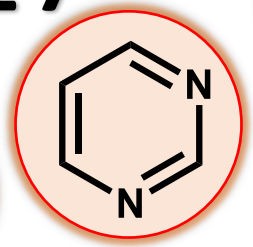
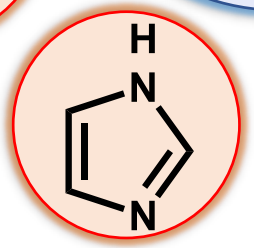
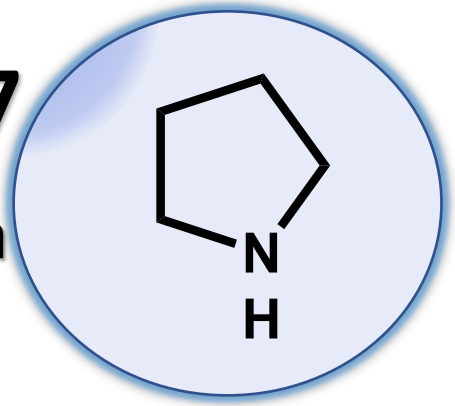


24

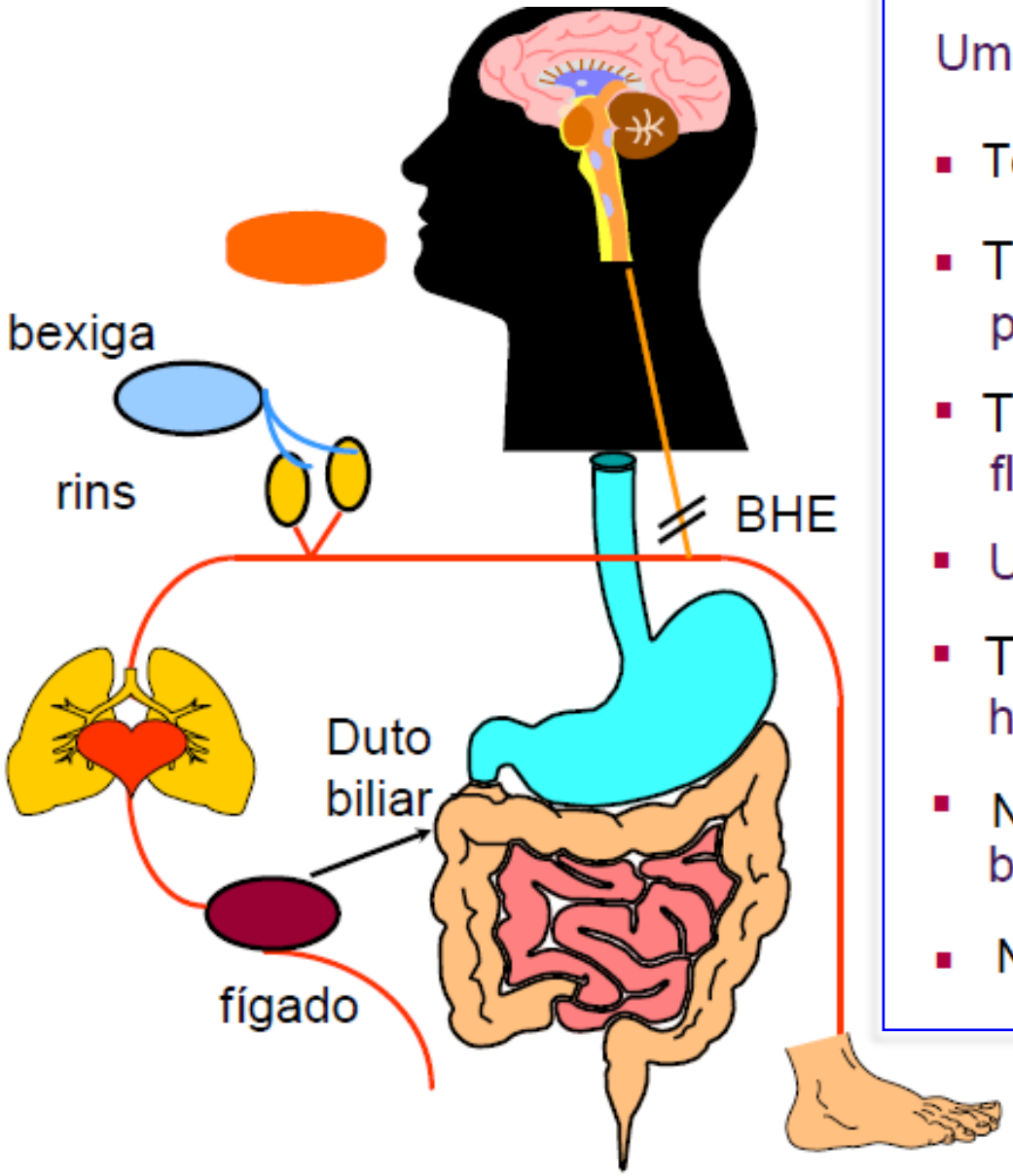


pirrolidina

37



Propriedades desejadas num fármaco



Um fármaco oral deve:

- Ter boa dissolução na biofase
- Ter estabilidade em diferentes pHs (1.5 a 8.0)
- Ter estabilidade com a flora intestinal
- Ultrapassar membranas
- Ter estabilidade metabolismo hepático
- Não sofrer transporte ativo pela bile
- Não permear tecidos indesejados


PD
PK
Potência
& Seletividade
Propriedades PFQ
PK / Posologia
Challenge
Química
Medicinal
LASSBio

THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

NATURE REVIEWS | DRUG DISCOVERY VOLUME 3 | OCTOBER 2004 | 853

Joseph G. Lombardino and John A. Lowe III‡*

"As a scientist involved at the very earliest stages of drug discovery, the medicinal chemist……

INTERDISCIPLINARY TEAMS

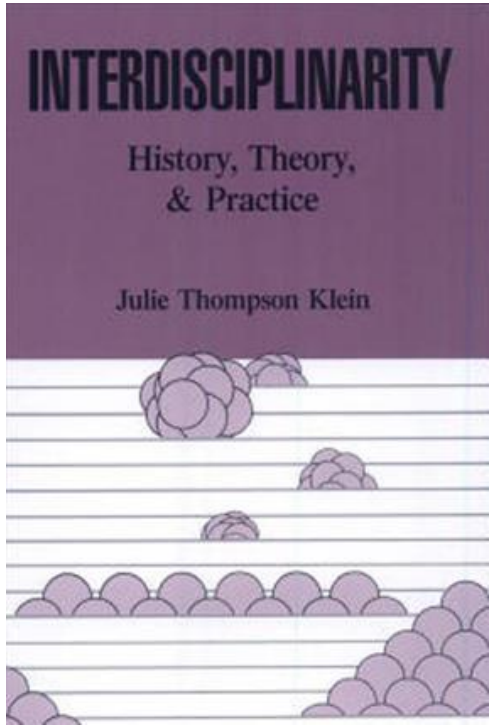
The role of pharmacology in drug discovery

NATURE REVIEWS | DRUG DISCOVERY VOLUME 1 | MARCH 2002 | 237

Bertil B. Fredholm, William W. Fleming, Paul M. Vanhoutte and Théophile Godfraind

"It is obvious that pharmacology is one of the most important scientific disciplines that underpin research in drug discovery."

A *interdisciplinaridade* é ESSENCIAL



na **solução de problemas**

ou **desafios, complexos** !

⬇

Fármacos

Química Medicinal

Química Nova, 2017, 40, 694

Química Nova, 2007, 30, 1456

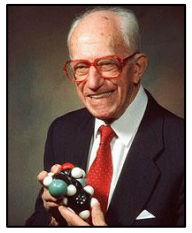
Estruturas Privilegiadas

Timeline das EP´s deste curso

1942 meperidina Demerol^{R}

1945 Univ. Cracóvia benzheptoxdiazinas

1950 Hoffmann-La Roche Leo Sternbach (1908-2005) BDZ



1958 J&J haloperidol

1963 Roche diazepan

1979 Pfizer piroxicam

1982 nifedipina

Paul A. J. Janssen (1926-2003) 4-fenilpiperidinas

1986 bifenila losartana AT_1-ant

2000 B&I meloxicam

1999 NAH

2006 paliperidona

2007 dasatinibe BMS

2010 Novartis pazopanibe

2011 Pfizer crizotinibe

2013 ponatinibe Ariad

maraviroque

Frontiers in Medcinal Chemistry

Privileged Structure

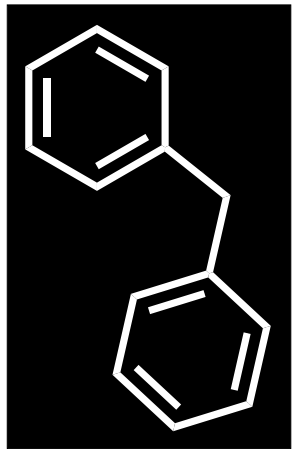
IUPAC

Substructural feature that confers desirable (often drug-like) properties on compounds containing that feature. They often consist of a semi-rigid *scaffold* that presents multiple hydrophobic residues

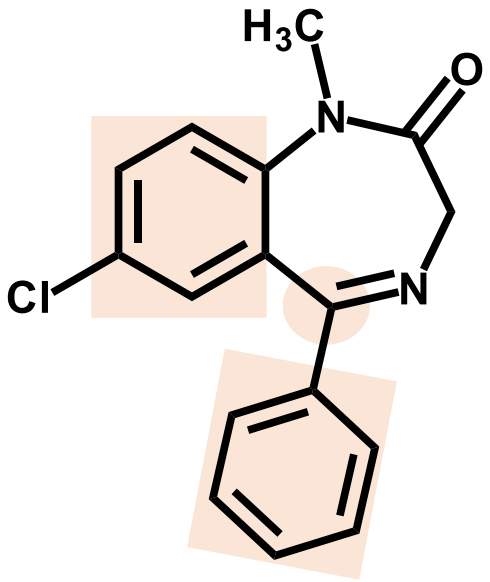
Note 1: For example, diazepam in which the diphenylmethane moiety prevents association of the aromatic rings.

GPCR's

Note 2: Such structures are commonly found to confer activity against different targets belonging to the same receptor family.



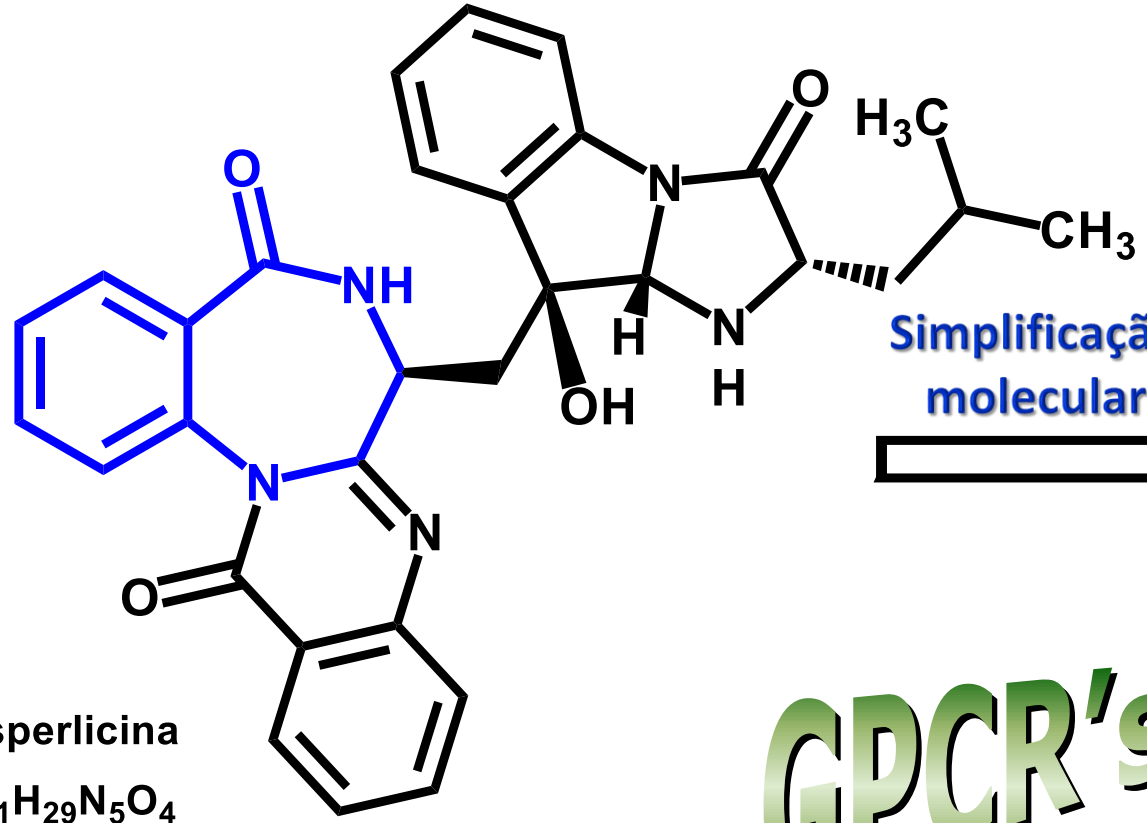
difenilmetano



Diazepam

B E Evans et al, Design of nonpeptidal ligands for a peptide receptor: cholecystokinin antagonists, *J Med Chem* **1987**, *30* (7), 1229.

Como surgiu o termo EP´s....



Asperlicina

$C_{31}H_{29}N_5O_4$

Micotoxina, CCK-AR ant

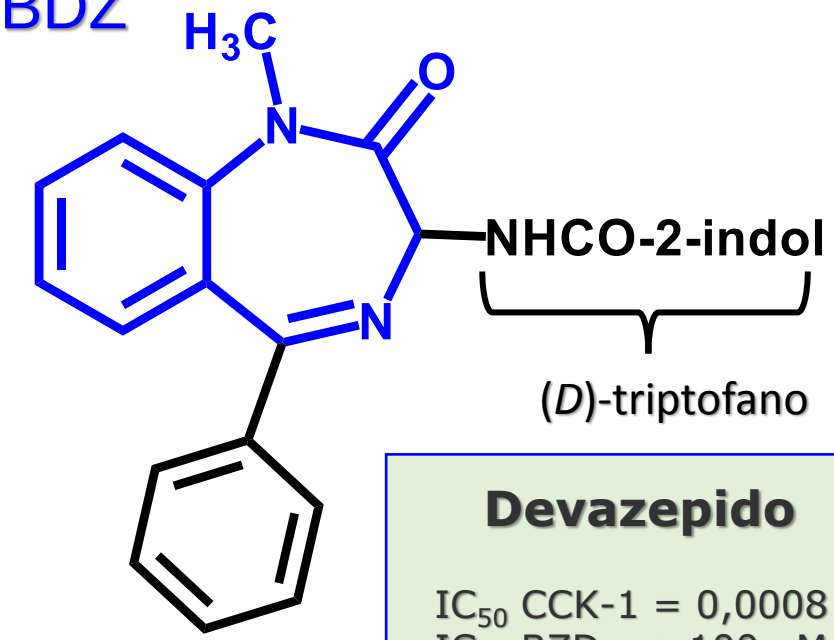
Colecistoquinina A

IC_{50} CCK-1 = 1,4 μM

Simplificação molecular

GPCR's

BDZ



(*D*)-triptofano

Devazepido

IC_{50} CCK-1 = 0,0008 μM

IC_{50} BZD = >100 μM

5-fenil-benzodiazepina

"Estrutura privilegiada"

⇩

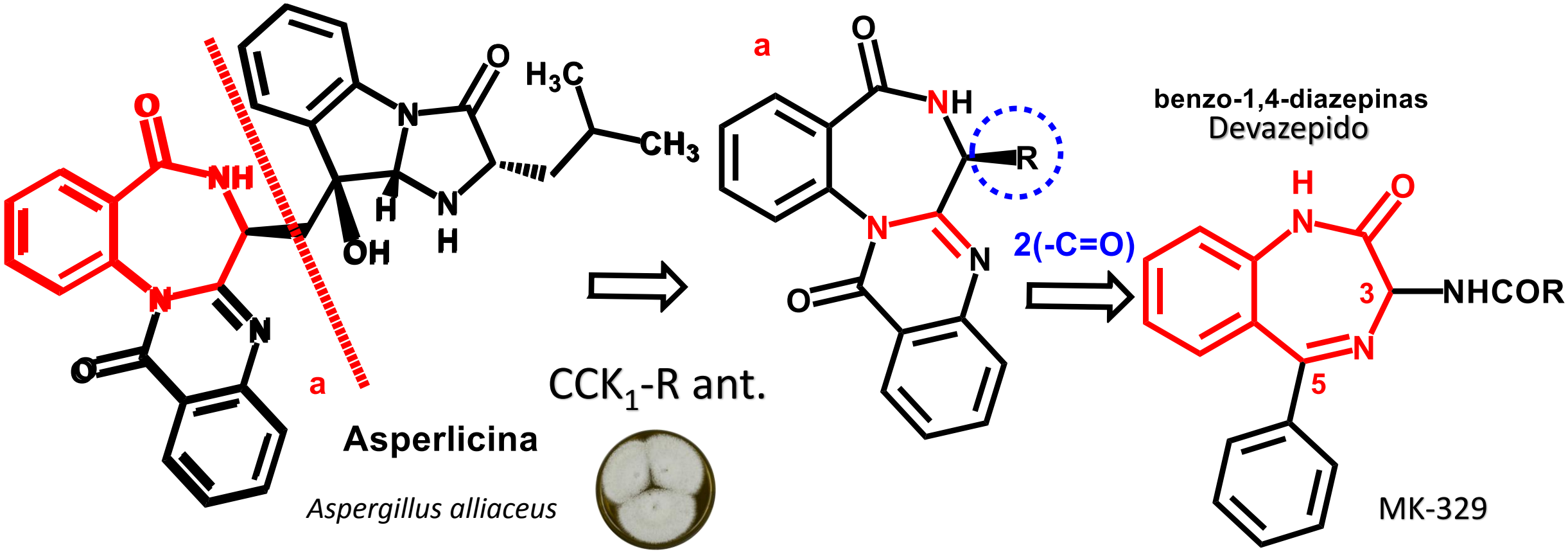
Vários biorreceptores

B E Evans et al. *Proc. Natl. Acad. Sci*. **1986**, *83*, 4918

B E Evans et al. *J. Med. Chem*. **1988**, *31*, 2235

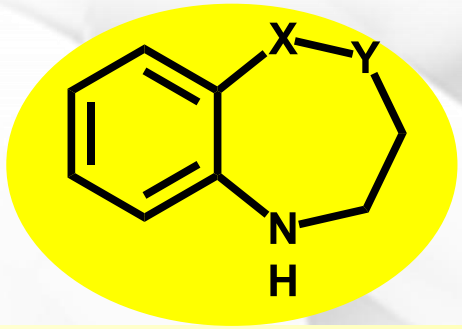
Da asperlicina a benzo-1,4-diazepinas

Dissecação Molecular



M G Bock et al. Cholecystokinin antagonists. Synthesis of asperlicin analogues with improved potency and water Solubility, *J Med Chem*. **1986**, *29* (10), 1941;
B E Evans et al, Design of nonpeptidal ligands for a peptide receptor: cholecystokinin antagonists, *J Med Chem* **1987**, *30* (7), 1229.

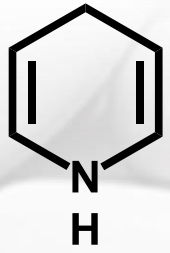
1950



X=CH_2 Y=NH - 1,4-benzodiazepinas

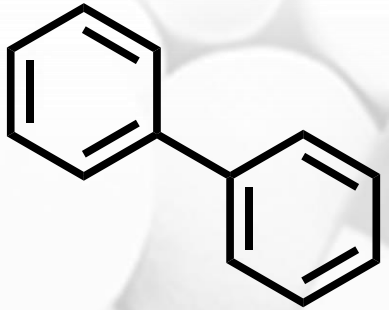
X=NH Y=CH_2 - 1,5-benzodiazepinas

1982



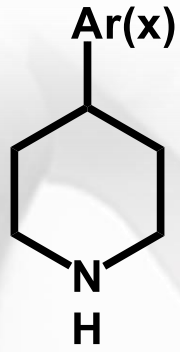
1,4-diidropiridinas

1986



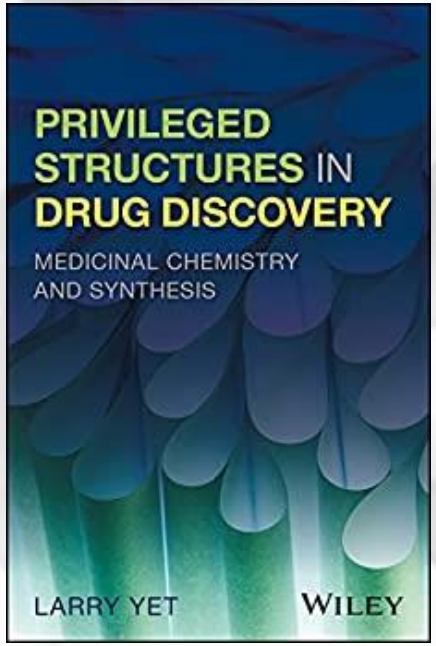
Bifenila

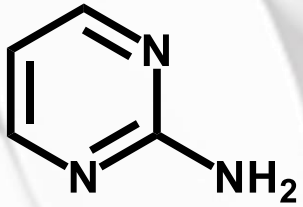
1958



4-arilpiperidinas

4-heteroarilpiperidinas

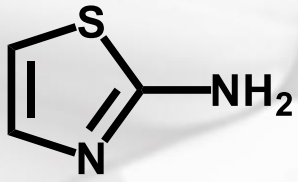




2-aminopirimidinas

crizotinibe

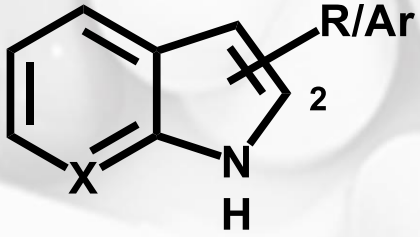
dasatinibe



2-aminotiazolas

dasatinibe

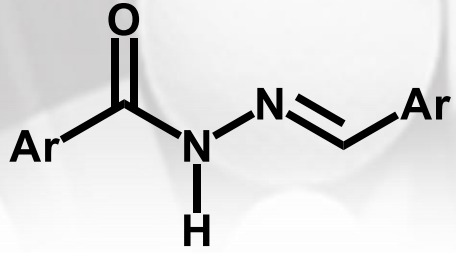
meloxicam



X=CH indol

X=N 7-azaindol

1999



N-acilidrazona

Os fármacos benzodiazepínicos

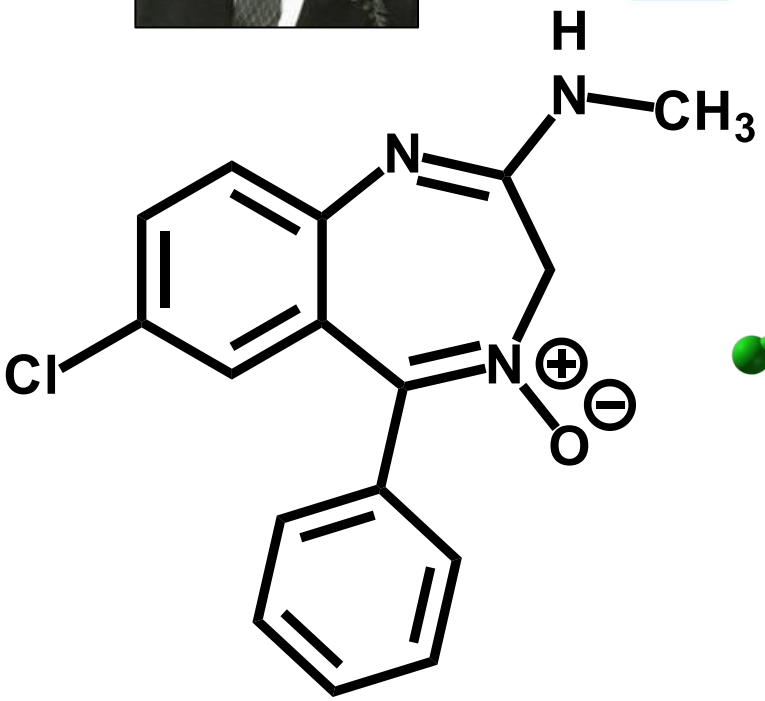
Leo H. Sternbach

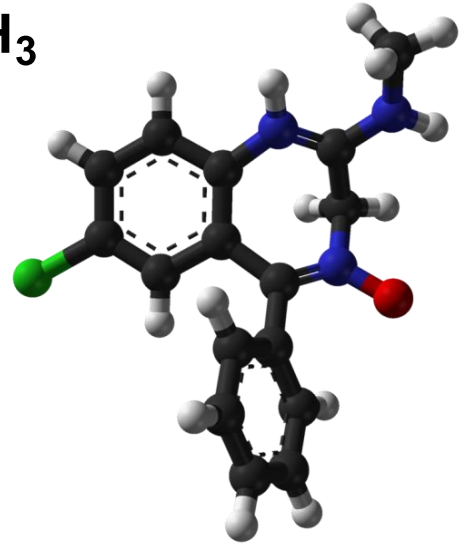
(1908-2005)

Roche 1950

"Serendipity"

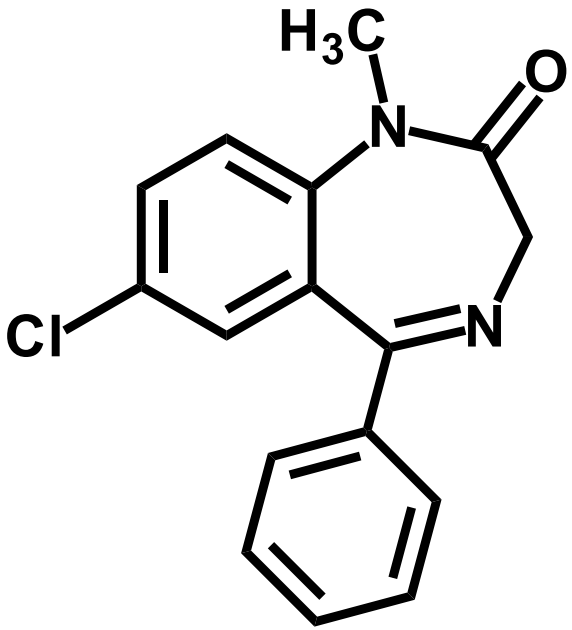
INOVAÇÃO Farmacêutica Pharma

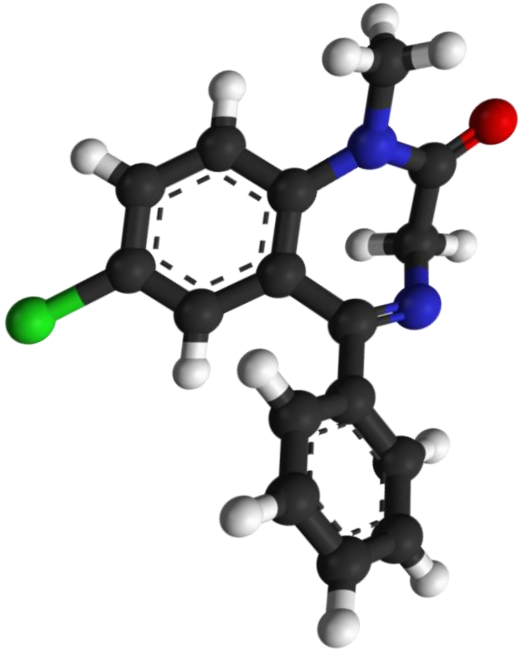




clordiazepóxido

Diazepam

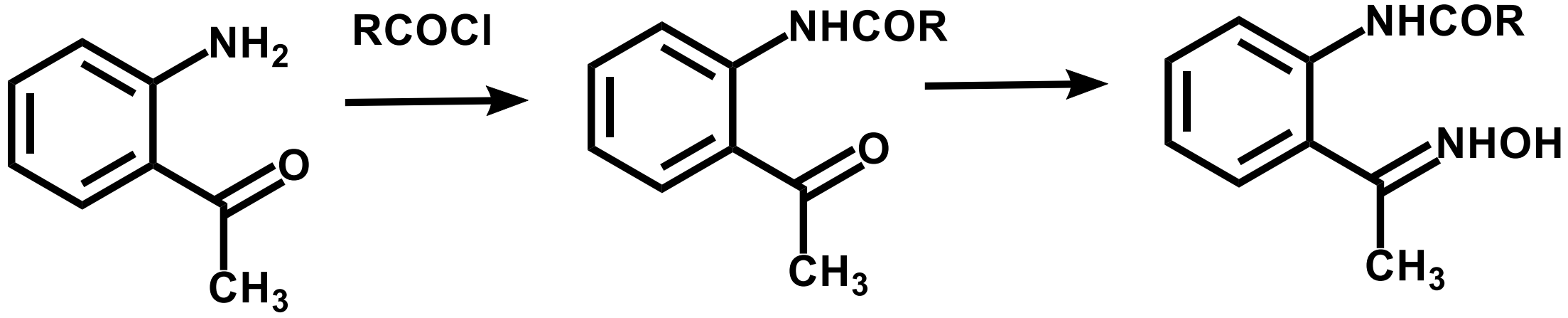




EVQFM - Curso Professor CAM Fraga

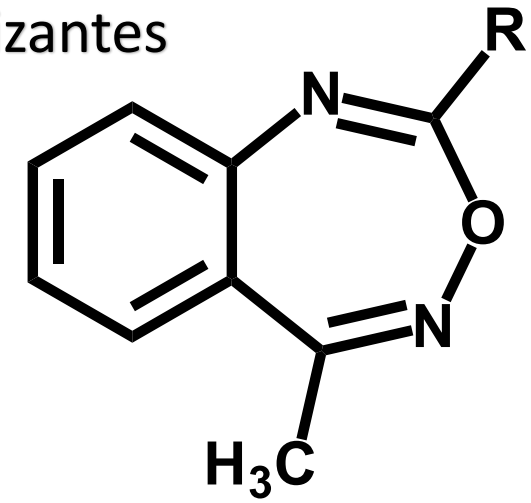
L H Sternbach, The benzodiazepine story, *J Med Chem* ***1979***, *22*, 1. doi: 10.1021/jm00187a001.

1891 - Auwers & Meyenburg



1946 - Estudos iniciais de Sternbach

1950 -Desenvolvimento de Novos Tranquilizantes



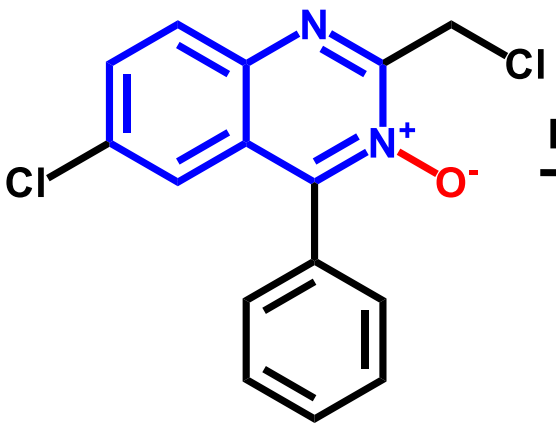
heptoxdiazinas

1924

não obtido

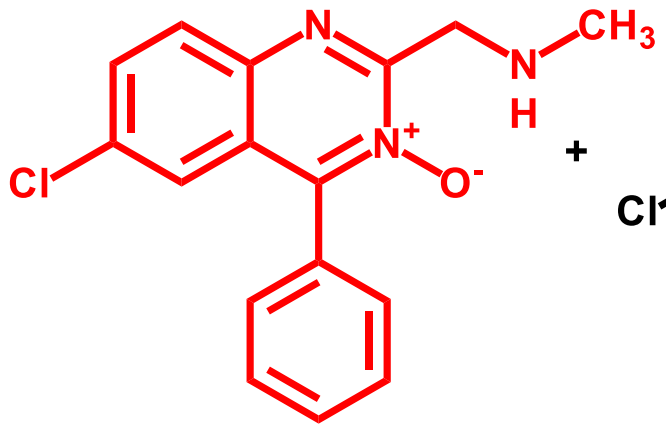
K Auwers, F v Meyenburg, *Chem. Ber.* **1891**, *24*, 2370, 2383, 2385.

1945 - Earl Reeder



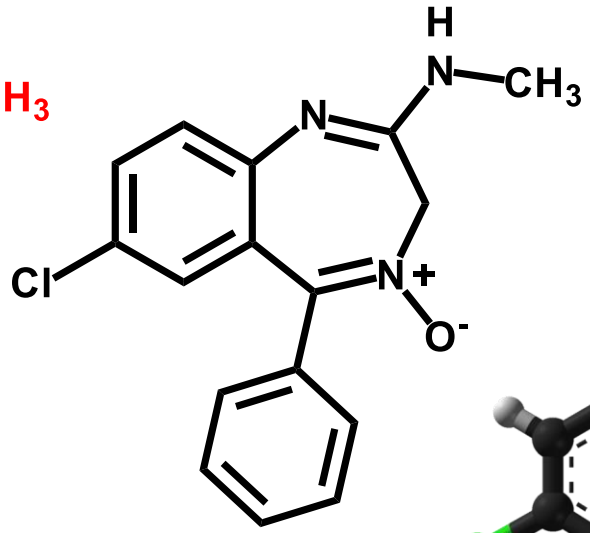
quinazolina *N*-óxido

$H_3C—NH_2$

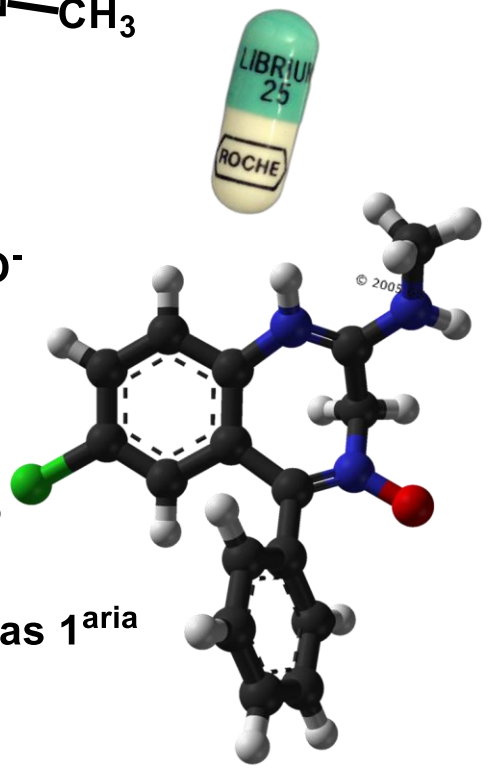


quinazolina *N*-óxido
produto esperado
majoritário aminas 2aria

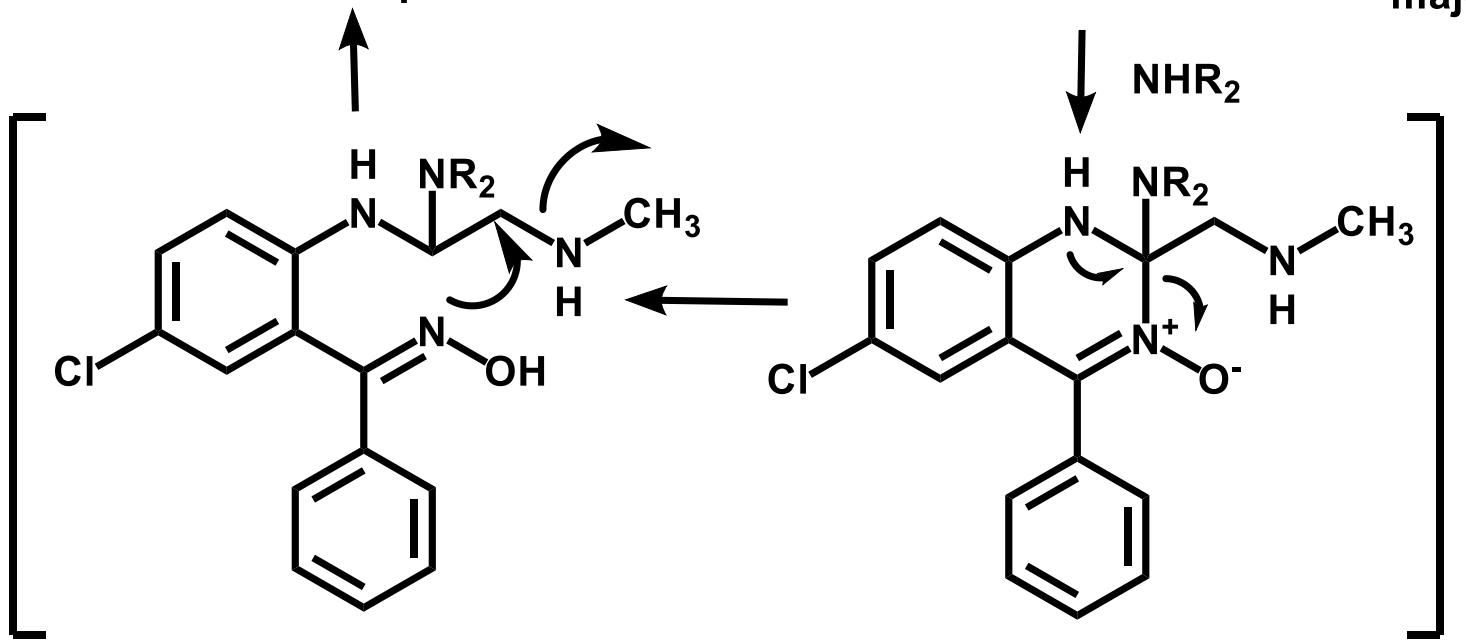
+



clordiazepóxido
produto obtido
majoritário com aminas 1aria



clordiazepóxido

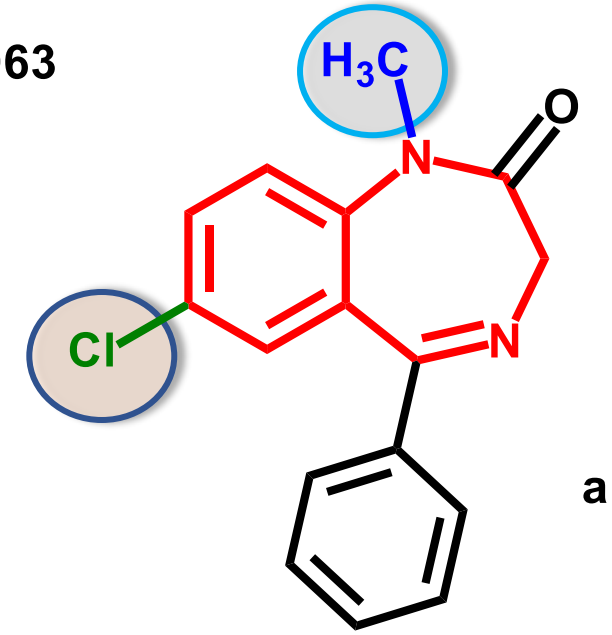


ATIVO
1957

INATIVOS
1950 - Beryl Campbell

Similaridade molecular

1963



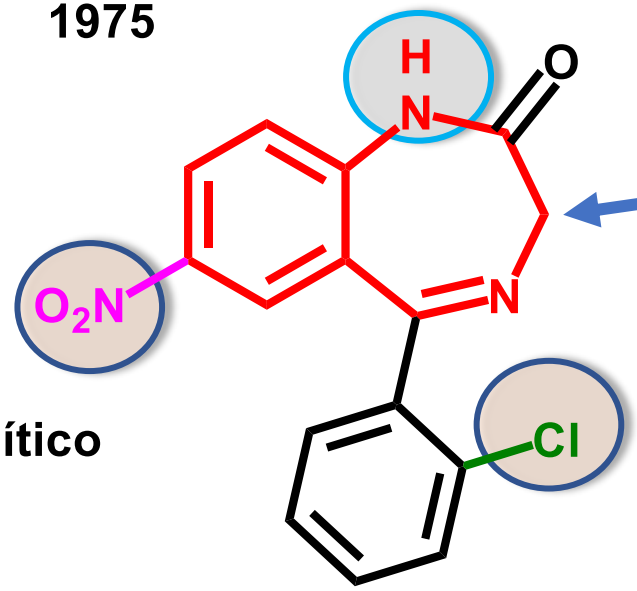
Diazepam

$GABA_{\alpha 5}$

IC_{50} (nM) 21,2

ansiolítico

1975

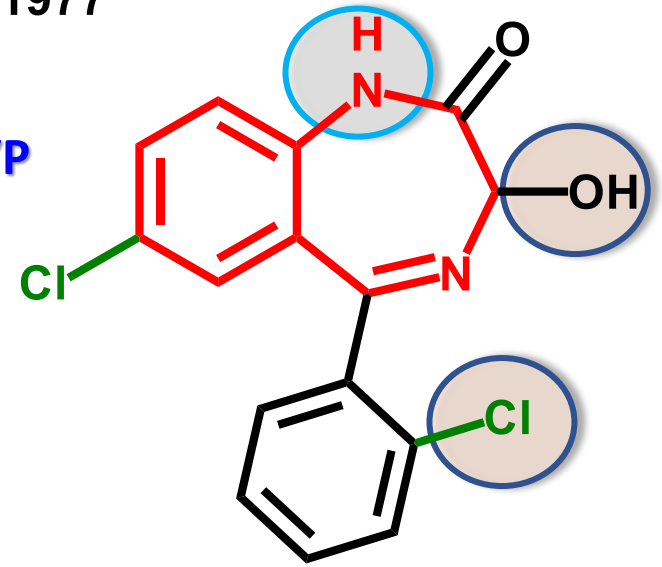


Clonazepam

Roche

CYP

1977

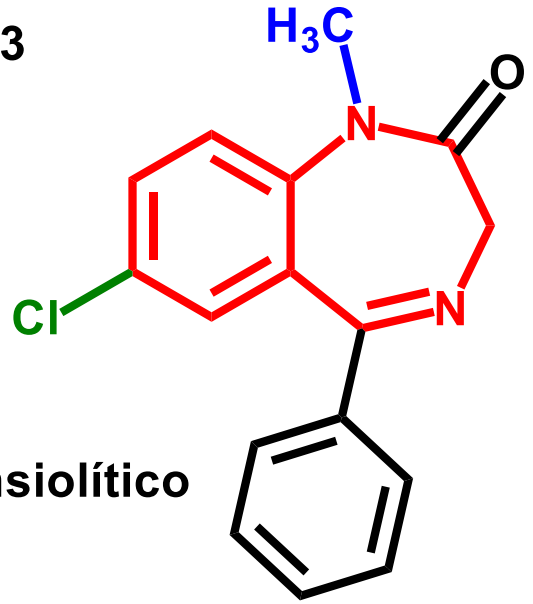


Lorazepam

Actavis

L H Sternbach, The benzodiazepine story, *J. Med. Chem*. **1979**, *22*, 1.

1963



ansiolítico

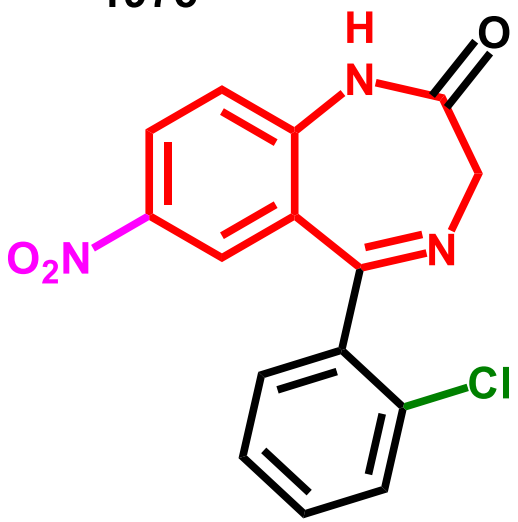
Diazepam

Valium^{R}

Roche

1,4-benzodiazepinas

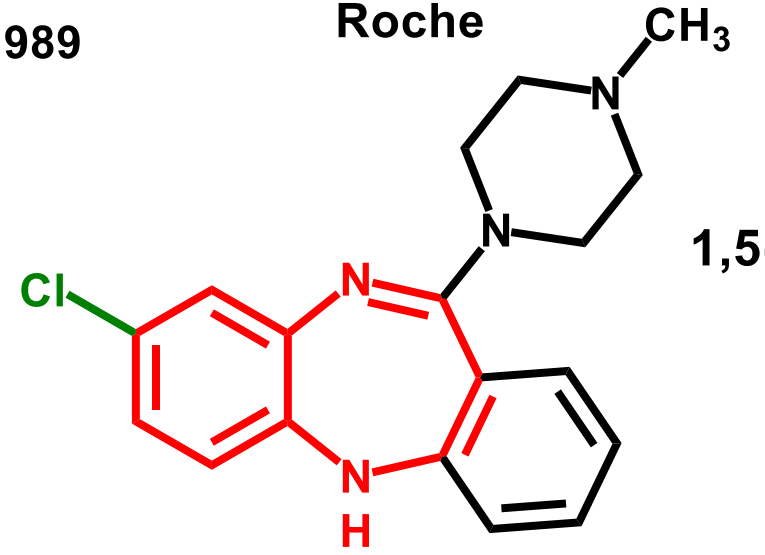
1975



Clonazepam

Roche

1989

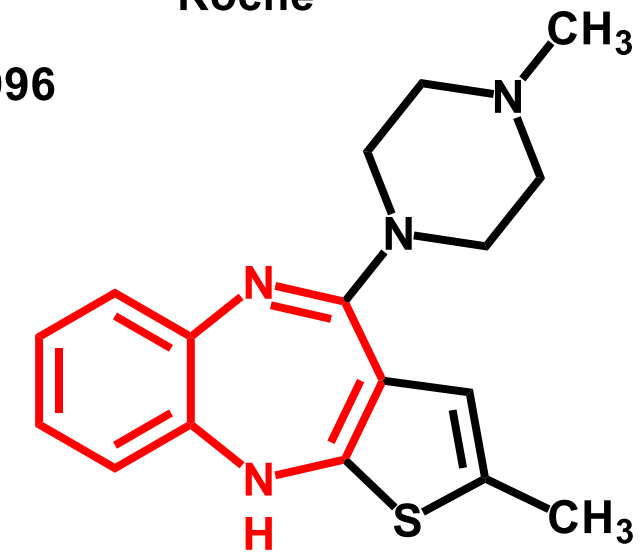


Clozapina

1,5-benzodiazepinas

antipsicótico
atipico

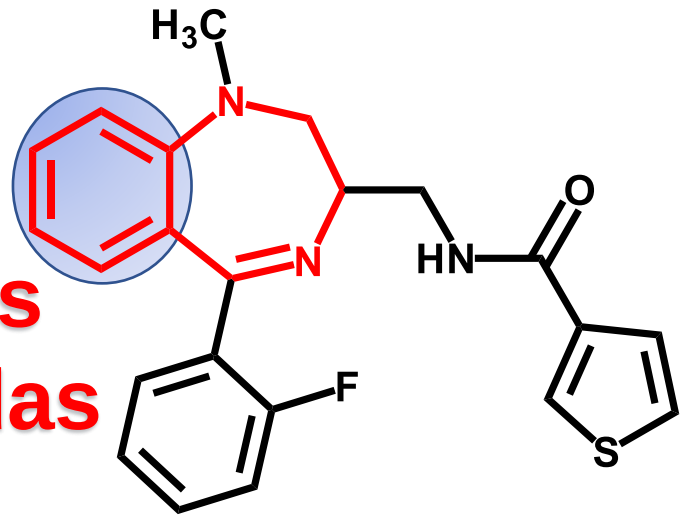
1996



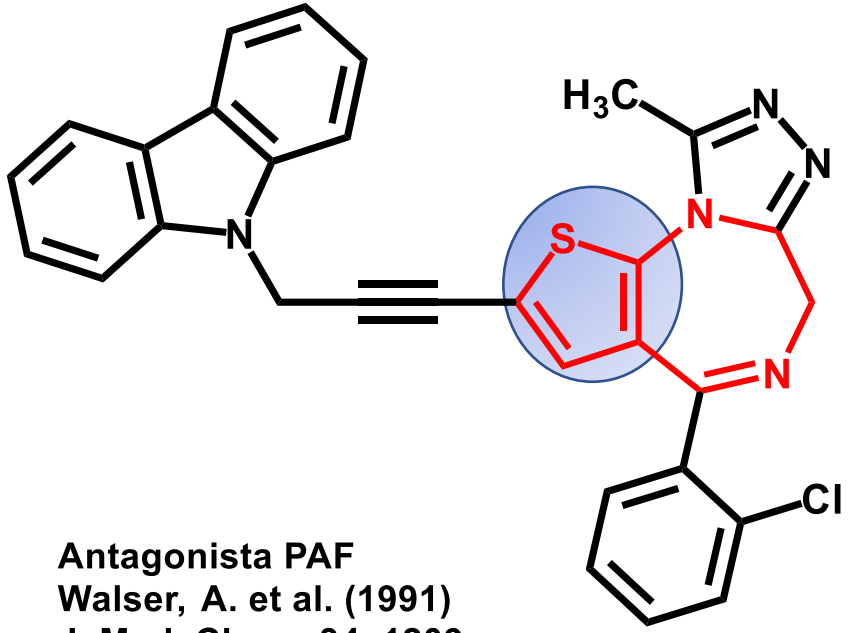
Olanzepina

Estruturas privilegiadas

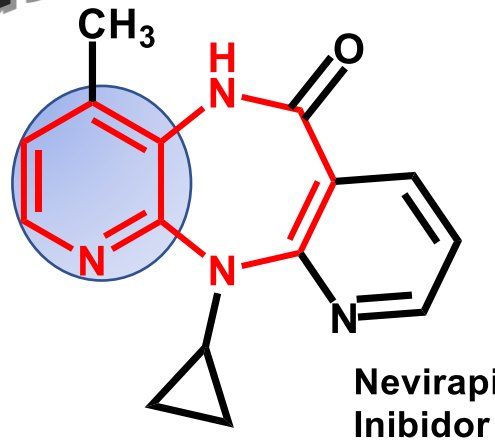
GPCR's e Enzimas



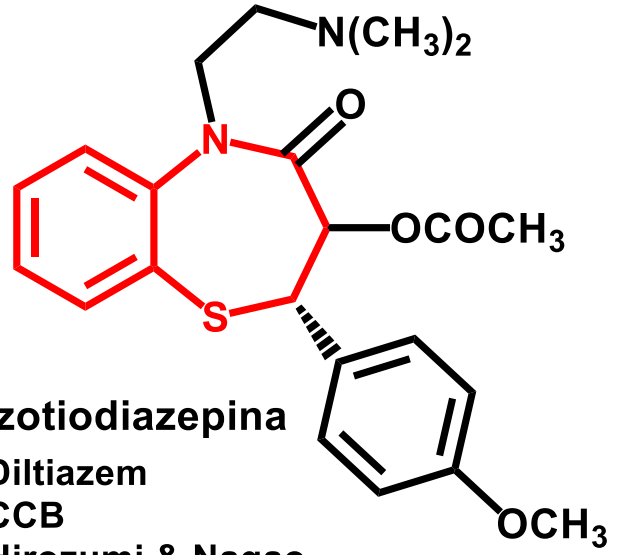
Tifluadom
Agonista ?-opióide
Römer, D. et al. (1982)
Nature 298, 759



Antagonista PAF
Walser, A. et al. (1991)
J. Med. Chem. 34, 1209



Nevirapine
Inibidor RT
Hargrave, K. D. et al. (1991)
J. Med. Chem. 34, 2231



1,5-benzotiodiazepina

Diltiazem
CCB
Hirozumi & Nagao,
Tanabe Co., 1974