Aula 11 – 05/08

Tópicos Especiais em Química Medicinal

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

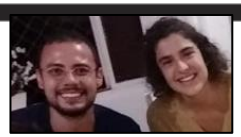
A intuição.....

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

REVIEW ARTICLE

BENTHAM SCIENCE

Chemical Intuition in Drug Design and Discovery



Júlia G.B. Pedreira[1,2], Lucas S. Franco[1,3] and Eliezer J. Barreiro[1,2,3,4,*]

[1]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Instituto de Ciências Biomédicas (ICB), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil;* [2]*Programa de Pós-Graduação em Química, UFRJ;* [3]*Programa de Pós-Graduação em Farmacologia e Química Medicinal, ICB-UFRJ, Rio de Janeiro, Brazil;* [4]*Programa de Pesquisas em Desenvolvimento de Fármacos (PPDF), ICB, UFRJ, Rio de Janeiro, Brazil*

ARTICLE HISTORY

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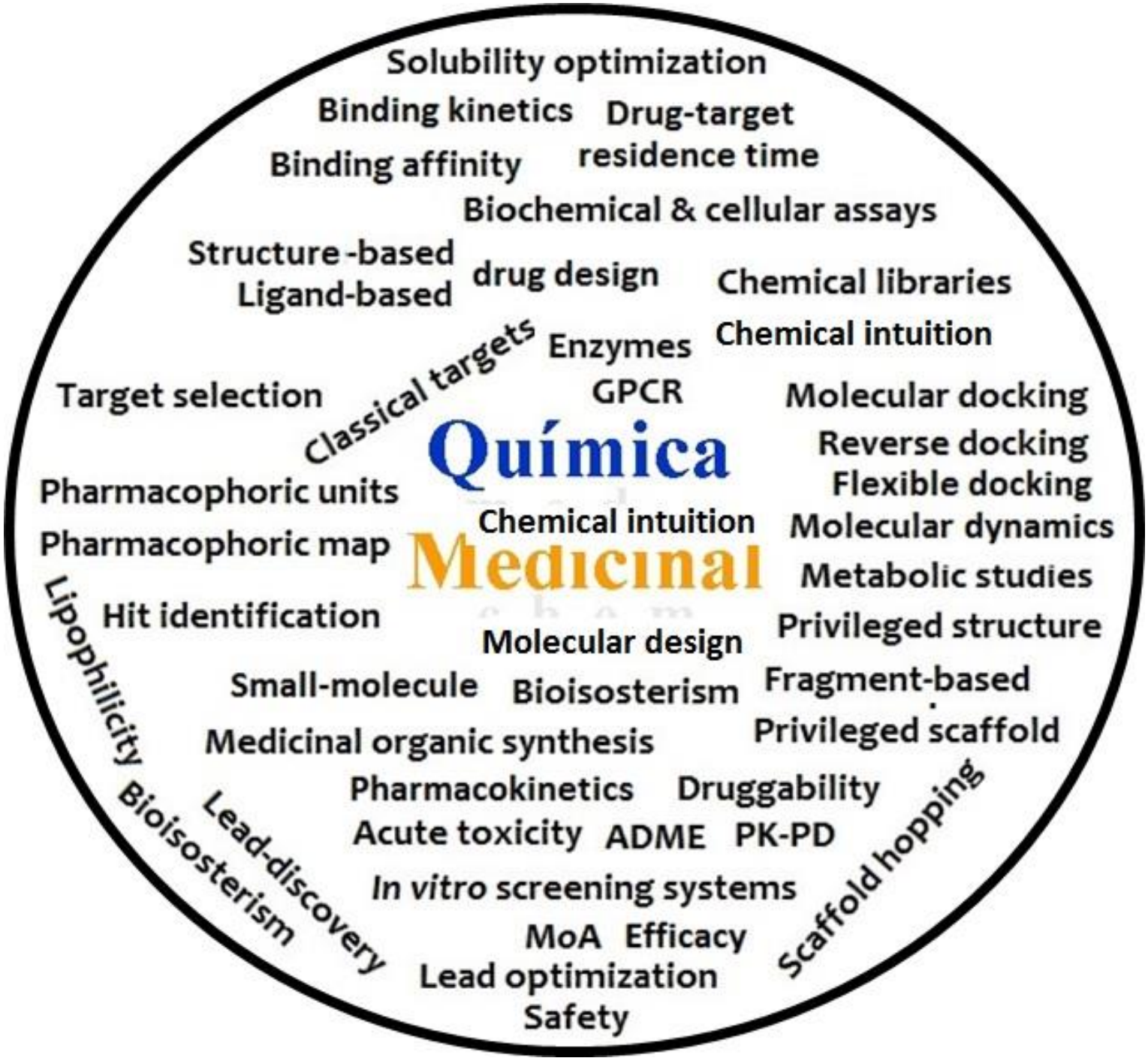
DOI:
10.2174/1568026619666190620144142

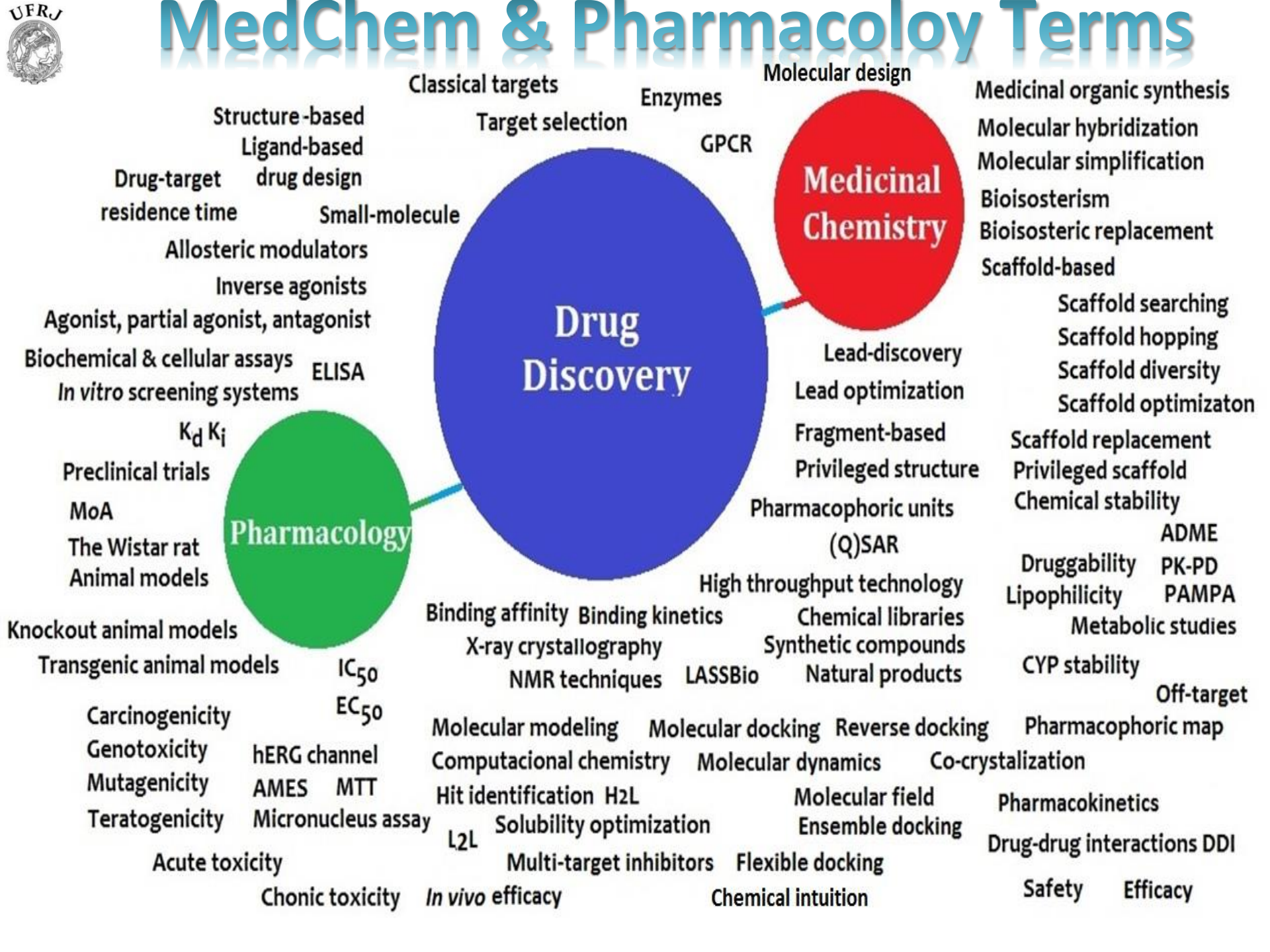
Abstract: The medicinal chemist plays the most important role in drug design, discovery and development. The primary goal is to discover leads and optimize them to develop clinically useful drug candidates. This process requires the medicinal chemist to deal with large sets of data containing chemical 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.

A Química Medicinal moderna


Solubility optimization
Binding kinetics
Drug-target residence time
Binding affinity
Biochemical & cellular assays
Structure-based drug design
Ligand-based
Chemical libraries
Chemical intuition
Classical targets
Enzymes
GPCR
Target selection
Molecular docking
Química
Reverse docking
Flexible docking
Pharmacophoric units
Chemical intuition
Molecular dynamics
Pharmacophoric map
Medicinal
Metabolic studies
Lipophilicity
Hit identification
Privileged structure
Molecular design
Small-molecule
Bioisosterism
Fragment-based
Privileged scaffold
Medicinal organic synthesis
Pharmacokinetics
Druggability
Bioisosterism
Lead-discovery
Acute toxicity
ADME
PK-PD
Scaffold hopping
In vitro screening systems
MoA
Efficacy
Lead optimization
Safety

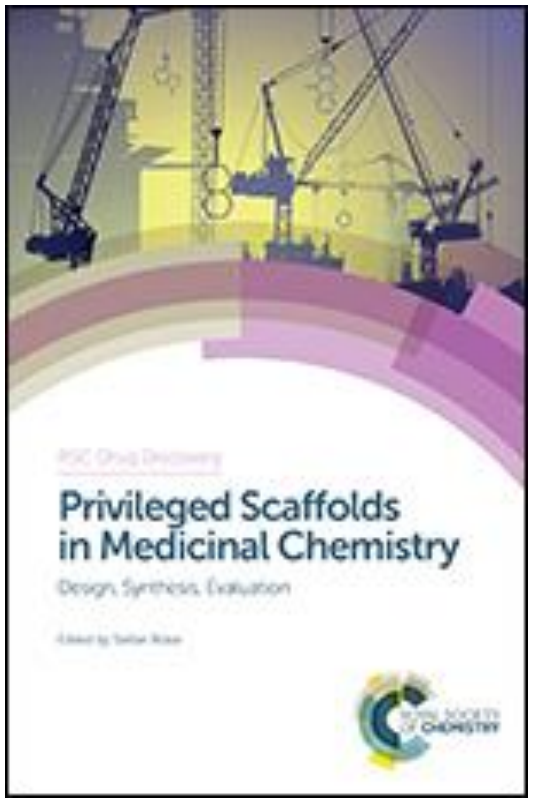
MedChem & Pharmacoloy Terms



Estruturas Privilegiadas

CHAPTER 1

Privileged Scaffolds in Medicinal Chemistry: An Introduction



ELIEZER J. BARREIRO

Laboratório de Avaliação e Síntese de Substâncias Bioativas, Universidade Federal do Rio de Janeiro, CCS, Cidade Universitária, PO Box 68.006, ZIP 21941-910, Rio de Janeiro, RJ, Brazil
Email: ejbarreiro@ccsdecania.ufrj.br

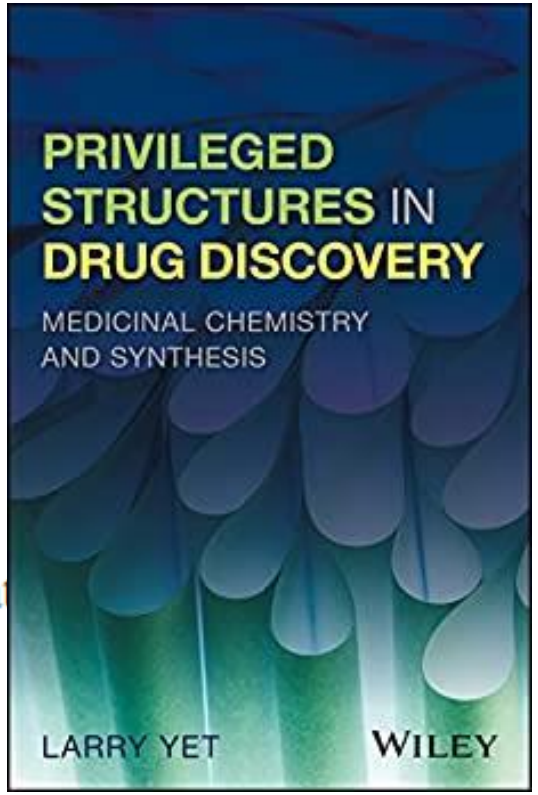
Chapter 1

London, 2016.

Stefan Bräse

Institute of Biological & Chemical Systems
Karlsruhe

Estruturas Privilegiadas



Mini-Reviews in Medicinal Chemistry, 2007, *7*, 1108-1119

Privileged Structures: A Useful Concept for the Ra
Lead Drug Candidates

Carolina D. Duarte, Eliezer J. Barreiro and Carlos A.M. Fraga*

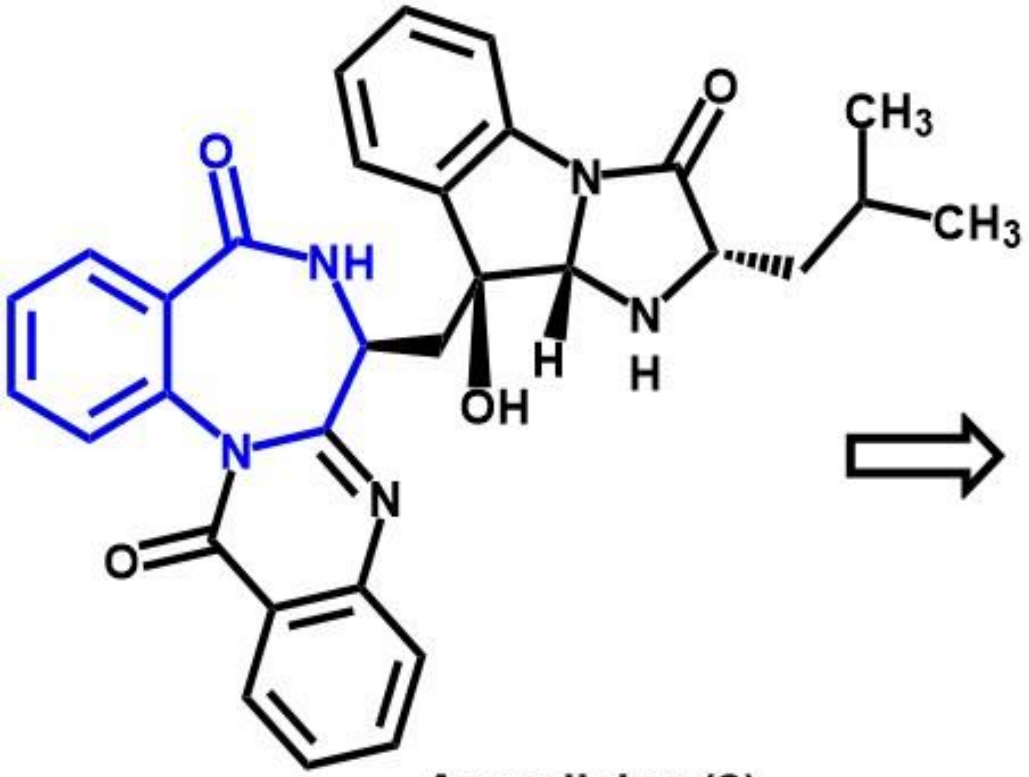
Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio, http://www.farmacia.ufrj.br/lassbio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, ZIP 21944-971, Rio de Janeiro, RJ, Brazil

Abstract: *Privileged structures* are defined as molecular frameworks which are able of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications. In the present work, we describe some examples and applications of the usefulness of the *privileged structure* concept for the structural design of new drug candidates, by discussing the eligibility of such motifs, including the identification of the *N*-acylhydrazone template as *privileged structures*.

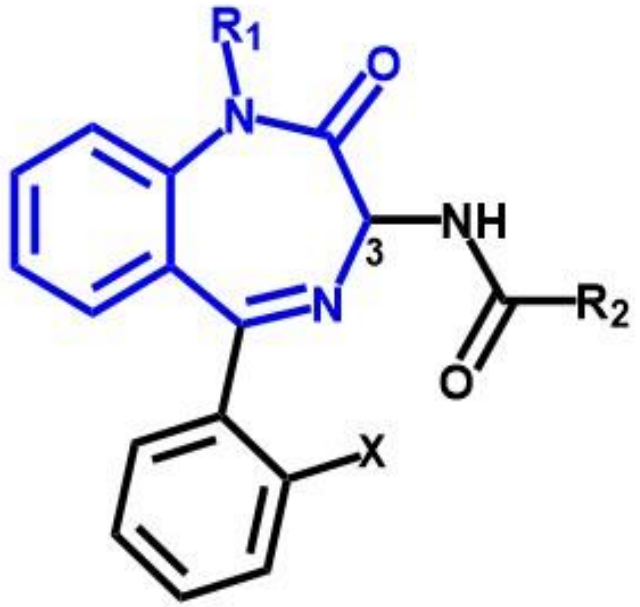
Key Words: Privileged structures, pharmacophoric point, rational drug design, bioactive *N*-acylhydrazones derivatives.

B E Evans, et al. *J Med Chem*, **1988**, *31*, 2235; A A Patchett, R P Nargund, *Annu Rep Med Chem,* **2000**, *35*, 289.

Estruturas privilegiadas



Asperlicina (2)



3-amidobenzodiazepina (1)

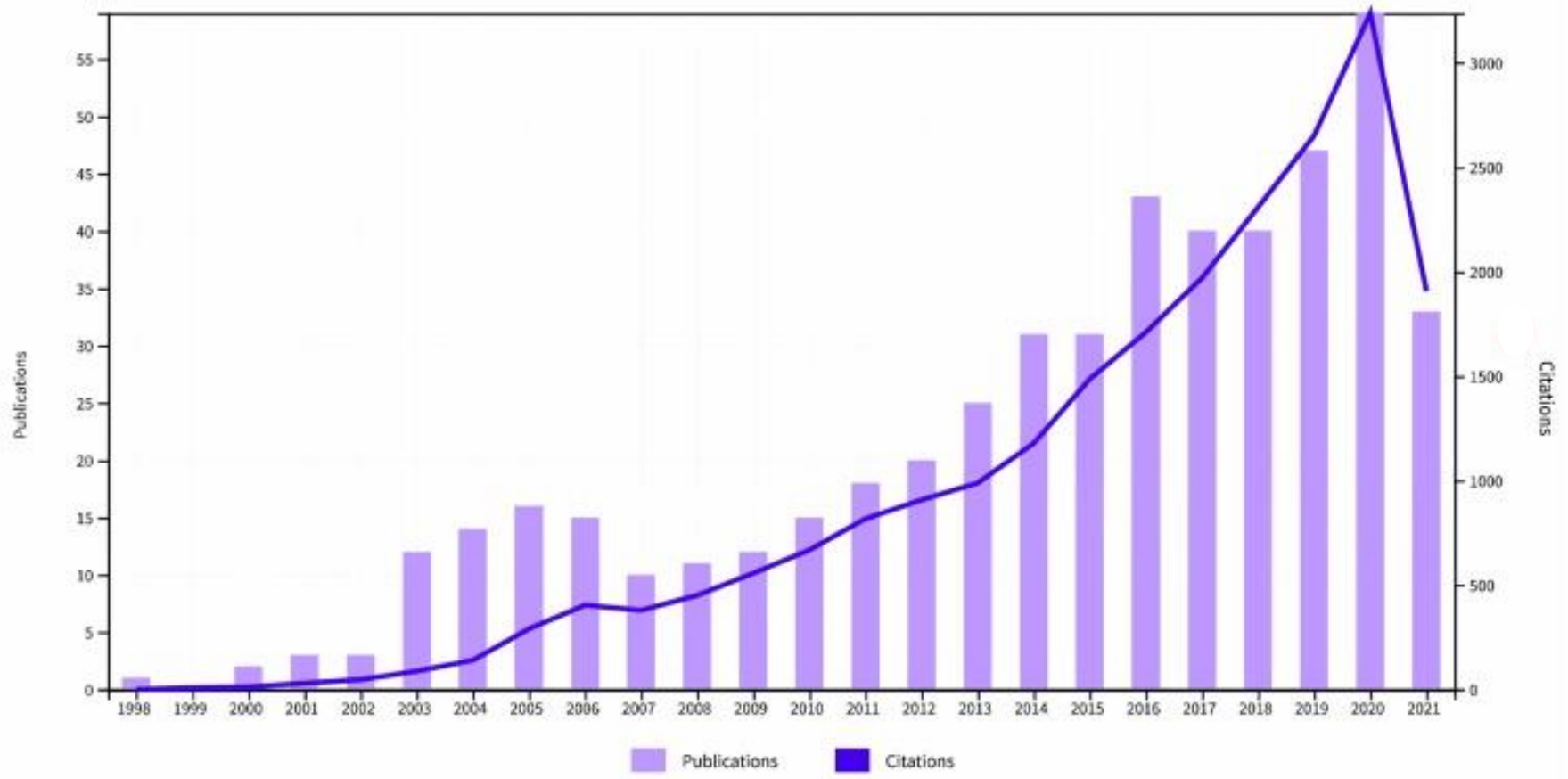
BE Evans et al. Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists, *J. Med. Chem.* **1988**, *31*, 2235.

Chapter 26. Privileged Structures – An Update

Arthur A. Patchett and Ravi P. Nargund,
Merck Research Laboratories, Rahway, NJ 07065-0900

Introduction -The term "privileged structure" was introduced by B. Evans et al. (1) in describing their development of benzodiazepine-based CCK-A antagonists from the natural product lead asperlicin. In their definition a privileged structure such as a benzodiazepine "is a single molecular framework able to provide ligands for diverse receptors..." Benzodiazepines are found in several types of CNS agents and are in ligands of both ion channel and G-protein coupled receptors (GPCRs). In the latter category Evans et al. cited the analgesic tifluadom which has both analgesic activity and affinity for the CCK-A receptor. These authors pointed out that core structures from which multiple activities can be derived is a broadly recognizable phenomenon and cited a review by Ariens (2) in which a "hydrophobic double-ring system" was exemplified in a number of biogenic amine antagonists. These ring systems, many of which were 1,1-diphenylmethane variants, were considered not to bind to the same receptor sites..."to which the highly polar agonists bind. They must bind to accessory binding sites of a predominantly hydrophobic nature..." (2). Ariens (3) further elaborated on these concepts and Andrews and Lloyd (4) described a number of common topological arrangements in biogenic amine antagonists. In summarizing their successful use of benzodiazepines, Evans and colleagues concluded that "judicious modification of such structures could be a viable alternative in the search for new receptor agonists and antagonists" (1).

Publicações com “Estruturas Privilegiadas”

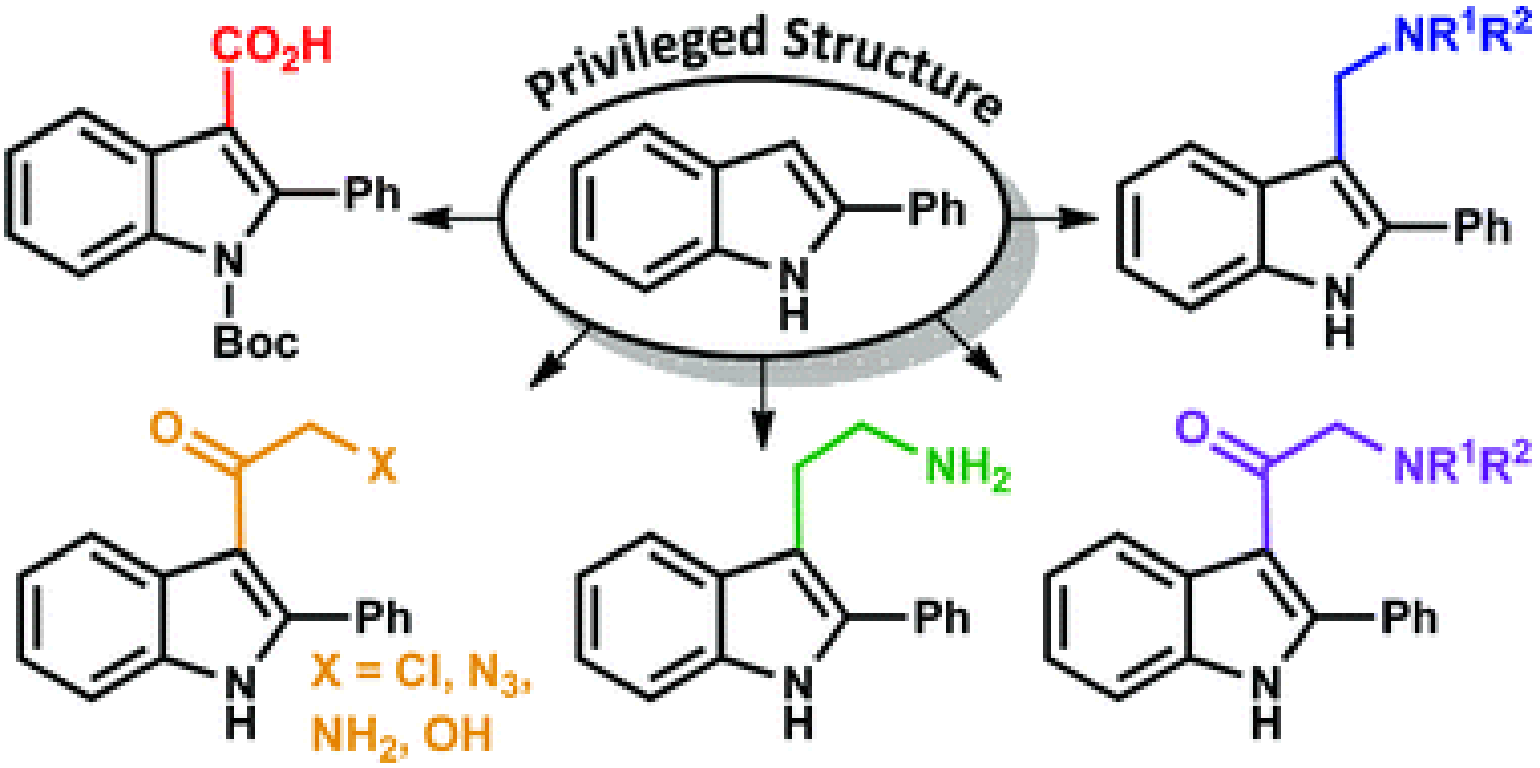


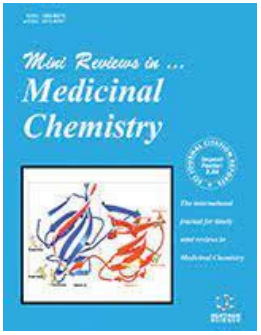
Webofscience, acessado em 25/07/2021

Soma do número de citações **22.242**

(H-index = 68)

Estruturas Privilegiadas





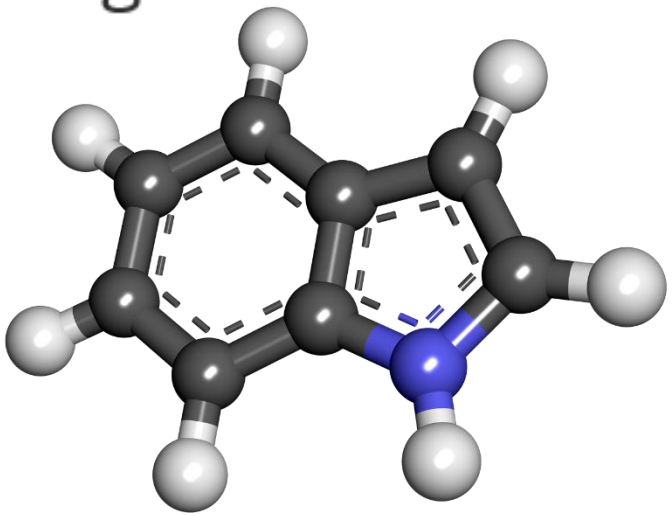
http://www.lassbio.icb.ufrj.br/

FR de Sá Alves, EJ Barreiro, CA Fraga, *Mini Rev. Med. Chem.*, **2009**, *9*, 782

Estruturas Privilegiadas

From Nature to Drug Discovery: The Indole Scaffold as a 'Privileged Structure'

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

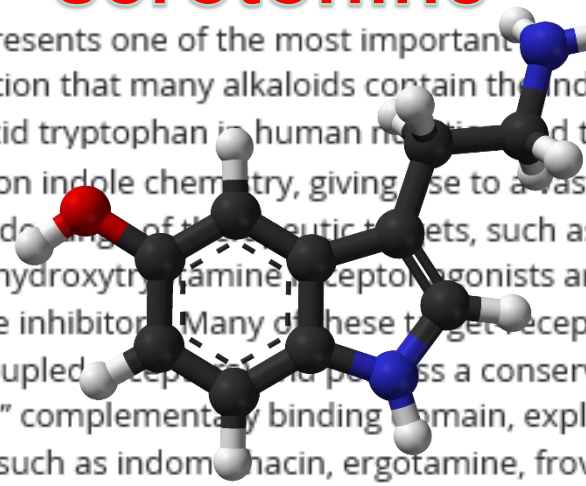


Authors: de Sa Alves, Fernando R.; Barreiro, Eliezer J.; Manssour Fraga, Carlos Alberto

Source: Mini Reviews in Medicinal Chemistry, Volume 9, Number 7, June 2009, pp. 782-793(12)

Publisher: Bentham Science Publishers

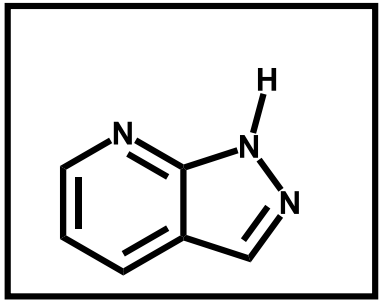
serotonine



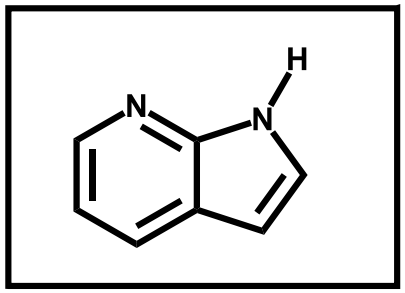
Abstract:

The indole scaffold probably represents one of the most important ural subunits for the discovery of new drug candidates. The demonstration that many alkaloids contain th ndole nucleus, the recognition of the importance of essential amino acid tryptophan in human n d the discovery of plant hormones served to bring about a massive search on indole chem try, giving se to a vast number of biologically active natural and synthetic products, with a wid of th eutic t ets, such as anti-inflammatories, phosphodiesterase inhibitors, 5-hydroxytr amine r ceptor gonists and antagonists, cannabinoid receptors agonists and HMG-CoA reductase inhibitor Many of these t get receptors belong to the class of GPCRs (integral membrane G-protein coupled ceptors) and possess a conserved binding pocket that is recognized by the indole scaffold in a "common" complementary binding domain, explaining the great number of drugs that contain the indole substructure, such as indomethacin, ergotamine, frovatriptan, ondansetron, tadalafil, among many others.

Estruturas Privilegiadas

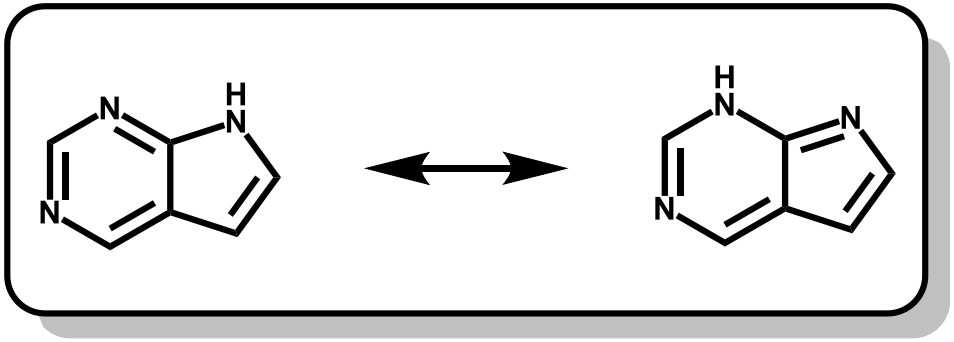


1H-pyrazolo[3,4-d]pyryidine



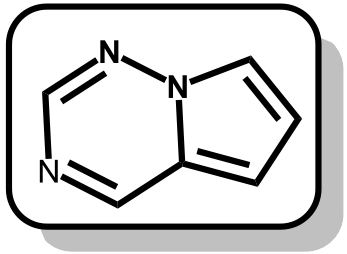
pyrrolo-pyridine

7-azaindole

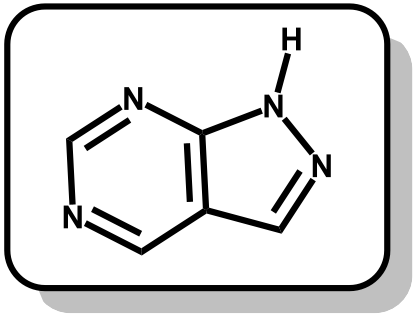


Pyrimido[4,5-*b*]indole

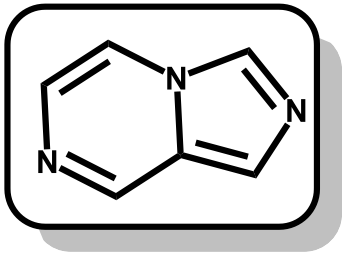
7*H*-Pyrrolo[2,3-*d*]-pyrimidine



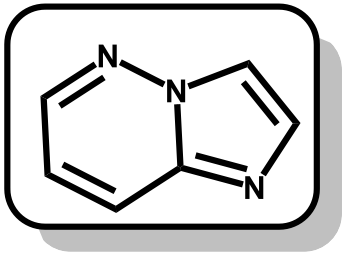
Pyrrolo[1,2-*f*][1,2,4]triazinepyrimidine



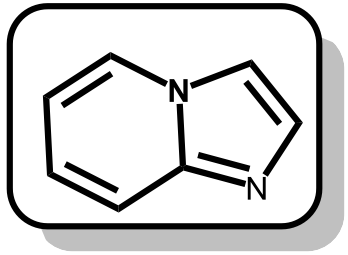
Pyrazolo[3,4-*d*]pyrimidine



Imidazo[1,2-*b*]pyrazine

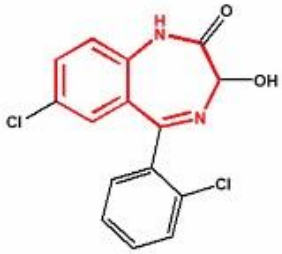


Imidazo[1,2-*b*]pyridazine

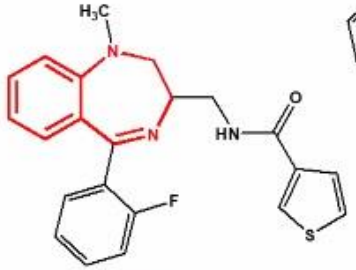


Imidazo[1,2*a*]pyridine

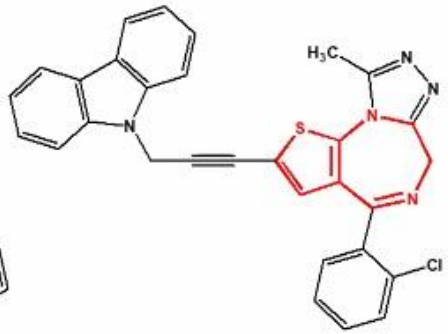
Estruturas privilegiadas como ligantes de GPCR´s e enzimas



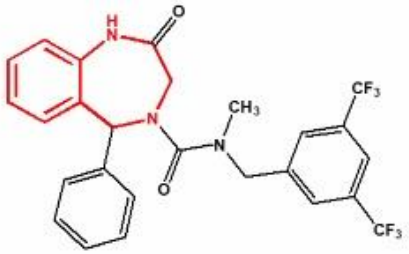
Lorazepam
Ansiolítico – BZD/GABA
Sternbach, L. E. (1979)
J. Med. Chem. 22, 1



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

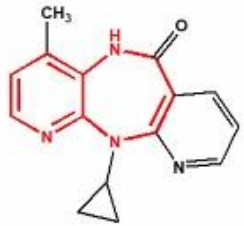


Antagonista PAF
Walser, A. *et al.* (1991)
J. Med. Chem. 34, 1209

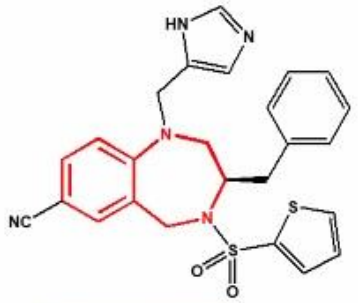


Antagonista NK-1
Armour, D. R. *et al.* (1997) *Bioorg. Med. Chem. Lett.* 7, 2037

Antagonista GPIIbIIIa
McDowell, R. S. *et al.* (1994)
J. Am. Chem. Soc. 116, 5077



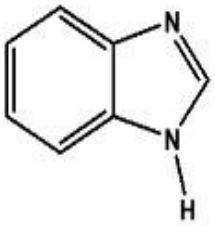
Nevirapine
Inibidor RT
Hargrave, K. D. *et al.* (1991)
J. Med. Chem. 34, 2231



BMS-214662
Inibidor Ras-Farnesil transferase
Hunt, J. T. *et al.* (2000)
J. Med. Chem. 43, 3587

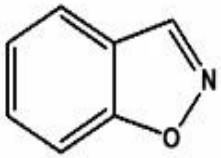
Estruturas Privilegiadas

Estruturas Privilegiadas



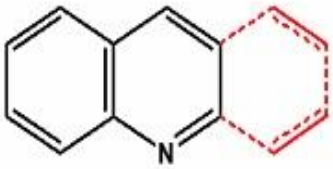
Benzimidazola

Shrivastava, N. et al. (2017) *Arch. Pharm.*, 350, e1700040.



Benzisoxazola

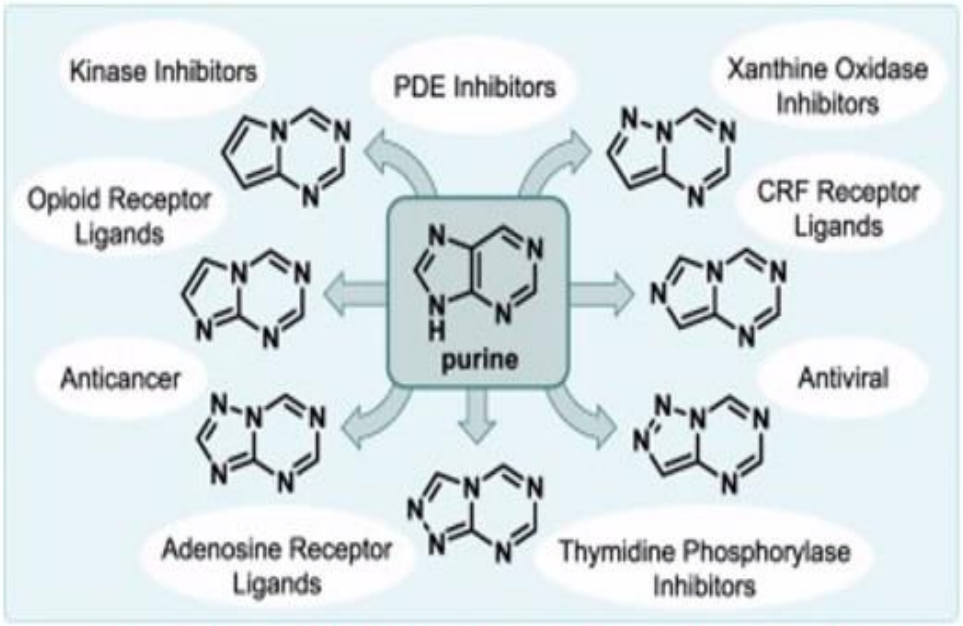
Rakesh, K. P. et al. (2017) *MedChemComm*, 8, 2023-39.



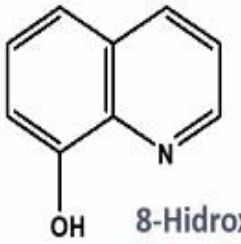
Quinolinas e Acridinas

Borgazone, S. & Bolognesi, M. L. (2011) *Expert Opin. Drug Discov.*, 6, 251-68.

Triazines

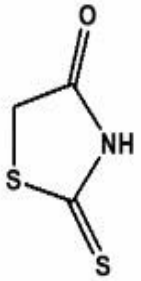


Lim, F. P. L. *et al.* (2014) *Eur. J. Med. Chem.* 85, 371-90.
Song, Y. et al. (2013) *Curr. Pharm. Des.*, 19, 1528-48.



8-Hidroxiquinolina

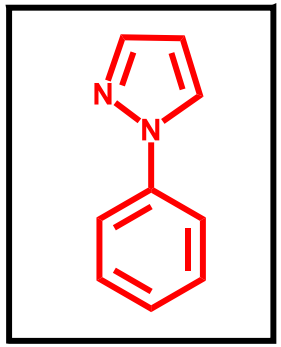
Song, Y. et al. (2015) *MedChemComm*, 6, 61-74.



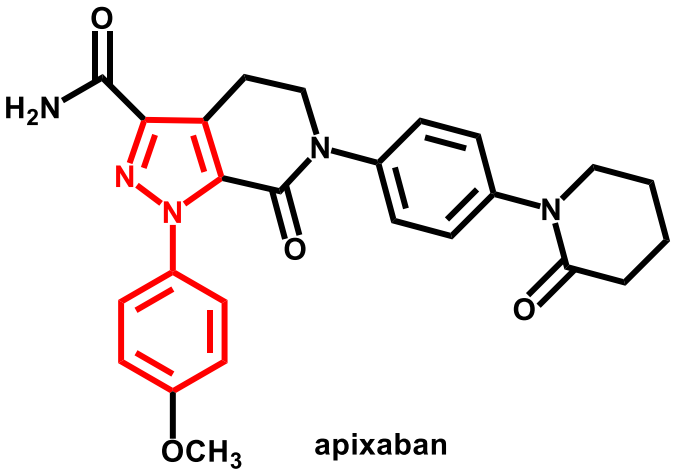
Rodanina

Tomasic, T. & Masic, L. P. (2012) *Expert Opin. Drug Discov.*, 7, 549-60.

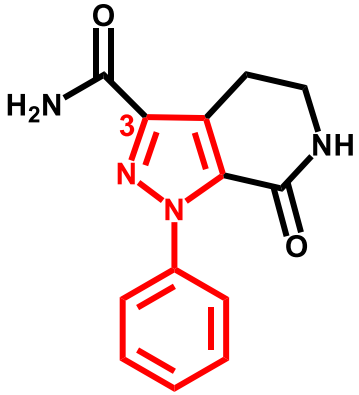
Combinando estratégias



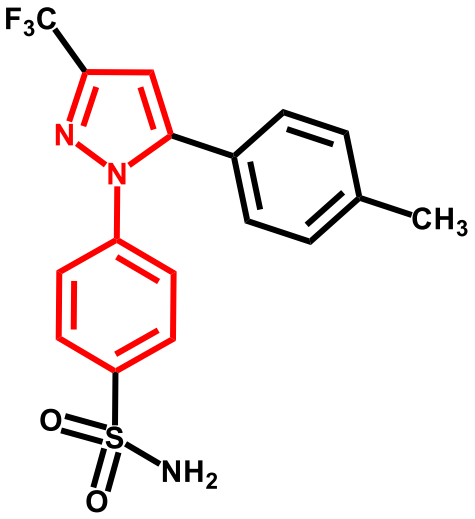
N-phenylpyrazole



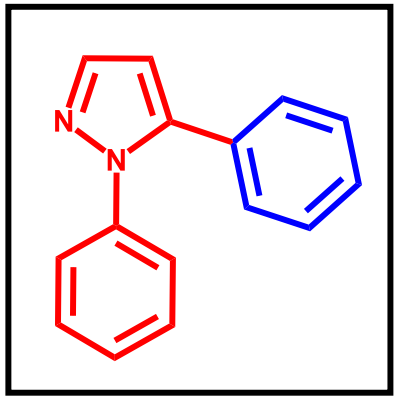
apixaban



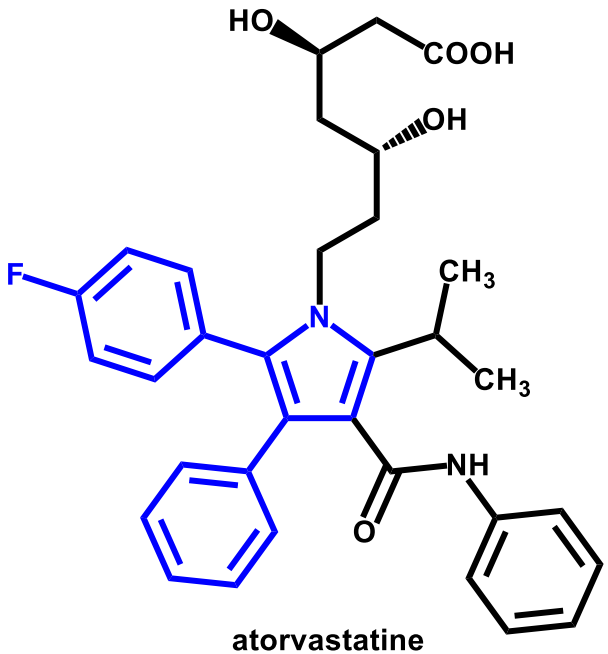
precursor



celecoxib



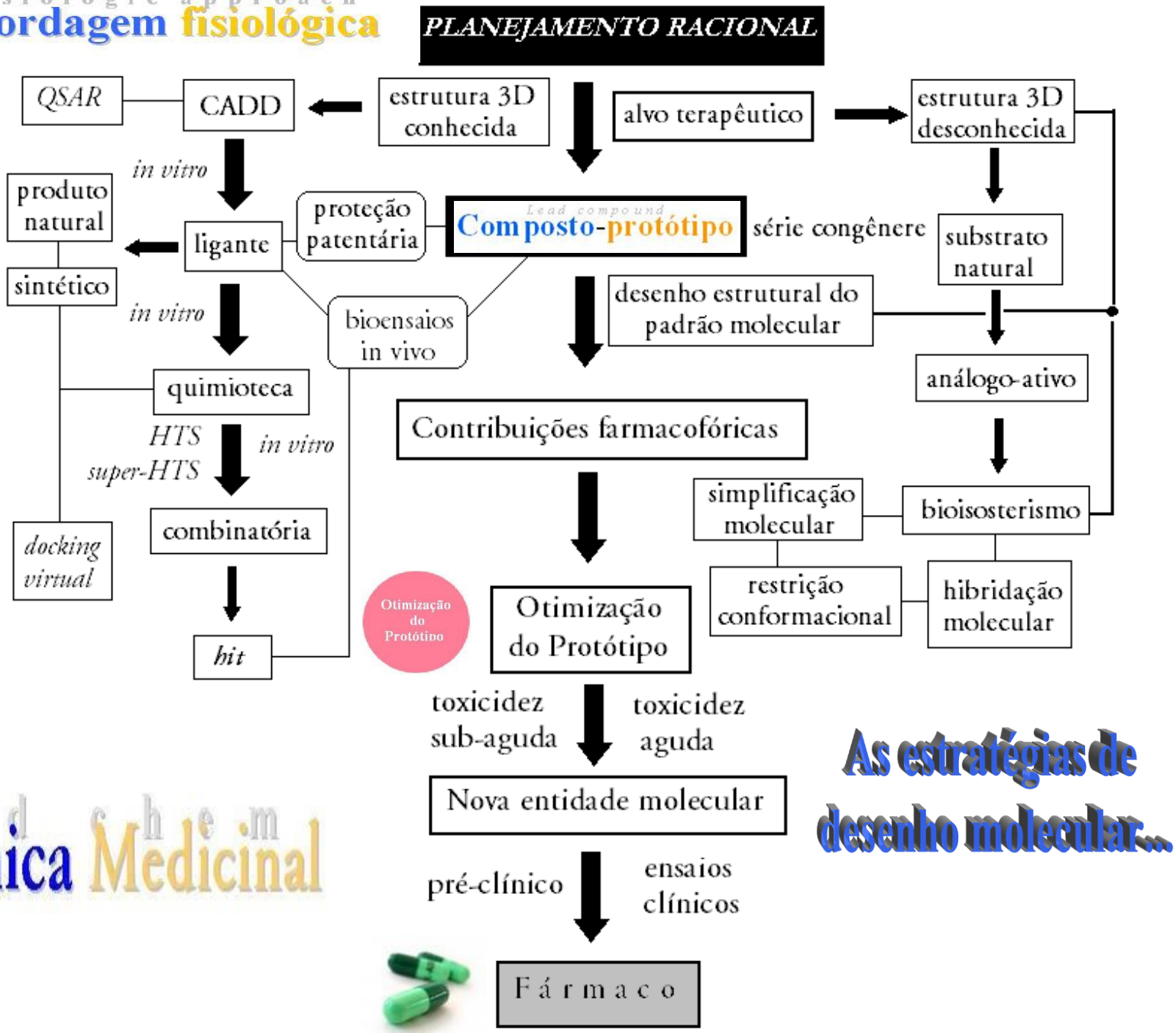
terphenyl scaffold



atorvastatine

Physiologic approach

A abordagem fisiológica



Química Medicinal

As estratégias de desenho molecular...